EXHIBIT 10

From: Stephen Kimmel
To: Mitchell, Allen A
Cc: Louik, Carol
Subject: Re: Question about NEJM paper
Date: Thursday, July 02, 2015 8:50:28 AM

Thank you Allen, I totally understand the nature of this and really appreciate your clarifying.

> Dear Steve,
>
> As you might imagine, the timing of our response cannot be driven by your court-related work. As it happens, we were able to retrieve the original files for the paper, and we did indeed err in transcribing the CI for the adjusted odds ratio for sertraline exposure in relation to septal defects (all of the other values in that table were correct). The point estimate (2.0) was correct, but the published CI of 1.2-4.0 should have been 1.0-4.0. We have notified the NEJM of the error, and they will publish a correction along with a corrected online version of the ms that reflects the change in CIs. Thanks for bringing this matter to our attention.
>
> Best,
>
> Allen
>
> **(Please note new telephone number)**
>
> Allen A. Mitchell, M.D.
> Director, Slone Epidemiology Center
> Professor of Epidemiology and Pediatrics
> Boston University Schools of Public Health and Medicine
> 1010 Commonwealth Avenue
> Boston, MA 02215
> allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119
>
> **From:** Stephen Kimmel [mailto:stevek@mail.med.upenn.edu]
> **Sent:** Wednesday, July 01, 2015 11:23 AM
> **To:** Mitchell, Allen A
> **Subject:** Re: Question about NEJM paper
>
> Hi Allen,
>
> Just wanted to check back on this. There is a court-imposed deadline of this coming Tuesday and I will likely be asked about this in court. If there is any way to get some clarification on this issue before then, I would greatly appreciate it. I am also happy to work with Carol directly on this.
>
> Thanks.
>
> > Sorry, Steve, for not responding more promptly. Your note came at a

particularly busy time, and I have not yet had a chance to discuss your request with Carol. I will get back to you when that has happened. Hope to see you in Boston in August.
Sent from my iPhone

On Jun 22, 2015, at 8:19 PM, Stephen Kimmel <stevek@mail.med.upenn.edu> wrote:

Re: Question about NEJM paper Hi Allen, just wanted to check to see if you got this email and to see if you might have some insights on this. I realize this is an older study and that it may be hard to clarify. Let me know what you think is possible if you can. Thanks.

Tuesday, June 16, 2015, 11:07:05 PM, you wrote:

Hi Allen, how are you? I am writing to ask you a question about your 2007 NEJM paper on SSRIs and birth defects. By way of disclosure, I have been serving as a consultant in litigation surrounding sertraline and birth defects.

My question relates to the OR and CI for sertraline and septal defects in Table 2 of the paper: 2.0 (1.2–4.0). When I plot this on a log scale, the CI is not symmetric. Also, the OR seems a bit high given the prevalence of exposure in the sertraline group.

Can you help me to clarify the results for sertraline and septal defects so I am clear that I have the correct numbers?

Thanks. Hope all is well.

-Steve

--
Stephen Kimmel, MD, MSCE
Professor of Medicine and Epidemiology
Director, Division of Epidemiology
Director, Center for Therapeutic Effectiveness Research
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA 19104-6021
stevek@mail.med.upenn.edu

--
- Steve

- Steve

- Steve

From: Mitchell, Allen A
To: Louik, Carol
Subject: RE: NEJM letter
Date: Tuesday, June 23, 2015 3:56:00 PM

My thoughts on the cover letter; I'll look at the NEJM "correction" next.

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
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allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Louik, Carol
Sent: Tuesday, June 23, 2015 3:45 PM
To: Mitchell, Allen A
Subject: NEJM letter

Proposed cover note to co-authors, draft of journal letter attached:

Dear co-authors

You may recall that in June, 2007 we published a paper in NEJM about SSRIs and birth defects. Allen recently received a note from a colleague (who has been retained as a legal expert) questioning one of the odds ratios and confidence intervals reported in that paper, specifically, the association between sertraline exposure and septal defects. Independent of the source of the question, Allen and I felt we needed to determine if we had made an error. I reviewed the analytic files that were used in preparing that paper and discovered that in fact there was an error in the results as reported in the paper—we reported an OR of 2.0 with 95% CI 1.2-4.0. The OR was correct, but the correct CI should have been 1.0-4.0. (The error resulted from a simple but unfortunate mistake in transcribing the results.) I rechecked all the other results in the table and this was the only one in error. This change would not affect any of the comments we made in the Discussion regarding risks of SSRIs.

We felt it would be appropriate for all of the original co-authors to sign a correction which we plan to send to NEJM and I've attached a draft of the letter we'd like to send. Please let me know if you are willing to cosign the letter; it would be great if you could let me know by next Wedn the end of next week (July2) so I can deal with this as promptly as possible.

I apologize to all of you for not catching this in the original paper.

Best,

Carol

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Mitchell, Allen A
To: Louik, Carol
Subject: RE: NEJM letter
Date: Tuesday, June 23, 2015 4:03:00 PM
Attachments: NEJM error.docx

I modified the letter a bit—didn't use track changes, but it's short enough for you to see the changes. It's really not a letter-to-the-editor, so I called it a "correction". If you're ok with the changes I suggested to both docs, send them to co-authors—I think giving them a week is enough; that way, if you don't hear by Wed, you have a couple days to call them.

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Louik, Carol
Sent: Tuesday, June 23, 2015 3:45 PM
To: Mitchell, Allen A
Subject: NEJM letter

Proposed cover note to co-authors, draft of journal letter attached:

Dear co-authors

You may recall that in June, 2007 we published a paper in NEJM about SSRIs and birth defects. Allen recently received a note from a colleague questioning one of the odds ratios and confidence intervals reported in that paper, specifically, the association between sertraline exposure and septal defects. I reviewed the analytic files that were used in preparing that paper and discovered that in fact there was an error in the results as reported in the paper—we reported an OR of 2.0 with 95% CI 1.2-4.0. The correct result is OR of 2.0 with 95% CI 1.0-4.0. I rechecked all the other results in the table and this was the only one in error. This change would not affect any of the comments we made in the Discussion regarding risks of SSRIs.

We felt it would be appropriate for all of the original co-authors to sign a letter to the editor describing this and I've attached a draft of the letter we'd like to send. Please let me know if you are willing to cosign the letter; it would be great if you could let me know by the end of next week (July2) so I can deal with this as promptly as possible..

I apologize to all of you for not catching this in the original paper.

Best,

Carol

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
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fax: 617-738-5119

Correction:

In response to an inquiry from a colleague regarding our paper "First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects" (NEJM ref), we discovered an error in Table 2. In that table, we reported an adjusted odds ratio for sertraline exposure in relation to septal defects as 2.0 with a 95% confidence interval of 1.2-4.0. On review of the original data tables, we confirmed that the odds ratio is correct as originally reported; however, due to a transcription error, the lower bound of the confidence interval should actually be 1.0 rather than 1.2. We have confirmed that all other entries in the table are correct as originally published.

We apologize for the error.

Sincerely,

Carol Louik etc.

From: Mitchell, Allen A
To: Hernandez-Diaz, Sonia
Cc: Louik, Carol
Subject: Re: error in NEJM paper
Date: Tuesday, June 23, 2015 6:32:01 PM

As Carol will likely explain, Steve Kimmel has been retained by lawyers – – probably for Pfizer, and likely in that case concerning septal defects and Zoloft. So he was motivated to look carefully at our estimates and confidence intervals, and his note indicated that he identified some asymmetry in the latter. When you're getting paid that kind of money, you have to earn it!
BTW, are you around over the next couple weeks?
Allen

Sent from my iPhone

On Jun 23, 2015, at 6:05 PM, Hernandez-Diaz, Sonia <shernan@hsph.harvard.edu> wrote:

> Thank you Carol,
> It is really impressive that a reader can catch an error in the CI, especially if there are different methods to estimating it that can give different results to the decimal point, and just the rounding of the estimate and the CI could explain another decimal.
>
> Yes, of course, I would be happy to sign.
> Best,
> s
>
> ---
>
> **From:** Louik, Carol [mailto:clouik@bu.edu]
> **Sent:** Tuesday, June 23, 2015 4:40 PM
> **To:** Angela Lin; Werler, Martha M; Hernandez-Diaz, Sonia; Mitchell, Allen A
> **Subject:** error in NEJM paper
>
> Dear co-authors
>
> You may recall that in June, 2007 we published a paper in NEJM about SSRIs and birth defects. Allen recently received a note from a colleague (who has been retained as a legal expert) questioning one of the odds ratios and confidence intervals reported in that paper, specifically, the association between sertraline exposure and septal defects. Independent of the source of the question, Allen and I felt we needed to determine if we had made an error. I reviewed the analytic files that were used in preparing that paper and discovered that in fact there was an error in the results as reported in the paper—we reported an OR of 2.0 with 95% CI 1.2-4.0. The OR was correct, but the correct CI should have been 1.0-4.0. (The error resulted from a simple but unfortunate mistake in transcribing the results.) I rechecked all the other results in the table and this was the only one in error. This change would not affect any of the

comments we made in the Discussion regarding risks of SSRIs.

We felt it would be appropriate for all of the original co-authors to sign a correction which we plan to send to NEJM and I've attached a draft of the letter we'd like to send. Please let me know if you are willing to cosign the letter; it would be great if you could let me know by next Wednesday (July 1) so I can deal with this as promptly as possible.

I apologize to all of you for not catching this in the original paper.

Best,

Carol

Carol Louik, Sc.D.
Assistant Professor
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1010 Commonwealth Ave.
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phone: 617-206-6208
fax: 617-738-5119

From: Hernandez-Diaz, Sonia
To: Louik, Carol; Angela Lin; Werler, Martha M; Mitchell, Allen A
Subject: RE: error in NEJM paper
Date: Tuesday, June 23, 2015 6:05:23 PM

Thank you Carol,
It is really impressive that a reader can catch an error in the CI, especially if there are different methods to estimating it that can give different results to the decimal point, and just the rounding of the estimate and the CI could explain another decimal.

Yes, of course, I would be happy to sign.
Best,
s

From: Louik, Carol [mailto:clouik@bu.edu]
Sent: Tuesday, June 23, 2015 4:40 PM
To: Angela Lin; Werler, Martha M; Hernandez-Diaz, Sonia; Mitchell, Allen A
Subject: error in NEJM paper

Dear co-authors

You may recall that in June, 2007 we published a paper in NEJM about SSRIs and birth defects. Allen recently received a note from a colleague (who has been retained as a legal expert) questioning one of the odds ratios and confidence intervals reported in that paper, specifically, the association between sertraline exposure and septal defects. Independent of the source of the question, Allen and I felt we needed to determine if we had made an error. I reviewed the analytic files that were used in preparing that paper and discovered that in fact there was an error in the results as reported in the paper—we reported an OR of 2.0 with 95% CI 1.2-4.0. The OR was correct, but the correct CI should have been 1.0-4.0. (The error resulted from a simple but unfortunate mistake in transcribing the results.) I rechecked all the other results in the table and this was the only one in error. This change would not affect any of the comments we made in the Discussion regarding risks of SSRIs.

We felt it would be appropriate for all of the original co-authors to sign a correction which we plan to send to NEJM and I've attached a draft of the letter we'd like to send. Please let me know if you are willing to cosign the letter; it would be great if you could let me know by next Wednesday (July 1) so I can deal with this as promptly as possible.

I apologize to all of you for not catching this in the original paper.

Best,

Carol

Carol Louik, Sc.D.
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Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Lin, Angela E.,M.D.
To: Louik, Carol; Werler, Martha M; shernan@hsph.harvard.edu; Mitchell, Allen A
Subject: RE: error in NEJM paper
Date: Tuesday, June 23, 2015 9:48:02 PM

Dear Carol,

Of course I would sign this.
Do you plan to recirculate and ask for actual signature?

Thanks,
Angela

From: Louik, Carol [mailto:clouik@bu.edu]
Sent: Tuesday, June 23, 2015 4:40 PM
To: Lin, Angela E.,M.D.; Werler, Martha M; shernan@hsph.harvard.edu; Mitchell, Allen A
Subject: error in NEJM paper

Dear co-authors

You may recall that in June, 2007 we published a paper in NEJM about SSRIs and birth defects. Allen recently received a note from a colleague (who has been retained as a legal expert) questioning one of the odds ratios and confidence intervals reported in that paper, specifically, the association between sertraline exposure and septal defects. Independent of the source of the question, Allen and I felt we needed to determine if we had made an error. I reviewed the analytic files that were used in preparing that paper and discovered that in fact there was an error in the results as reported in the paper—we reported an OR of 2.0 with 95% CI 1.2-4.0. The OR was correct, but the correct CI should have been 1.0-4.0. (The error resulted from a simple but unfortunate mistake in transcribing the results.) I rechecked all the other results in the table and this was the only one in error. This change would not affect any of the comments we made in the Discussion regarding risks of SSRIs.

We felt it would be appropriate for all of the original co-authors to sign a correction which we plan to send to NEJM and I've attached a draft of the letter we'd like to send. Please let me know if you are willing to cosign the letter; it would be great if you could let me know by next Wednesday (July 1) so I can deal with this as promptly as possible.

I apologize to all of you for not catching this in the original paper.

Best,

Carol

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.

Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Morrissey, Stephen
To: Mitchell, Allen A; Greene, Michael Furman,M.D.
Cc: Louik, Carol
Subject: RE: A question on process
Date: Wednesday, July 01, 2015 11:45:51 AM

The notice will be shorter and simpler – essentially "what appeared as 1.2 should have been 1.0." And we'll actually make the correction to the online version. You are welcome to let your colleague know.
Steve

Stephen Morrissey, Ph.D.
Managing Editor
New England Journal of Medicine
smorrissey@nejm.org
617-487-6552

From: Mitchell, Allen A [mailto:allenmit@bu.edu]
Sent: Wednesday, July 01, 2015 10:55 AM
To: Greene, Michael Furman,M.D.; Morrissey, Stephen
Cc: Louik, Carol
Subject: RE: A question on process

Many thanks! Steve—can I assume the content will appear as we wrote it, or will there be modifications?

Also, is there reason we can't inform now the colleague who brought the error to our attention that a correction will soon be published?

We appreciate your help, and do indeed sincerely regret the error!

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
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Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Greene, Michael Furman,M.D. [mailto:Greene.Michael@mgh.harvard.edu]
Sent: Wednesday, July 01, 2015 10:03 AM
To: 'Morrissey, Stephen'

Cc: Mitchell, Allen A; Louik, Carol
Subject: RE: A question on process

Steve, Thanks. Mike

Michael F. Greene MD
Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Vincent Department of Obstetrics and Gynecology
Massachusetts General Hospital
Boston, MA 02114
(617)724-9014
greene.michael@mgh.harvard.edu

From: Morrissey, Stephen [mailto:SMorrissey@nejm.org]
Sent: Wednesday, July 01, 2015 6:34 AM
To: Greene, Michael Furman,M.D.
Subject: RE: A question on process

We can handle it with a simple correction notice (no need for a published letter). All the relevant information is in the attachment you sent, so I'll put it into production.
Steve

From: Greene, Michael Furman,M.D. [mailto:Greene.Michael@mgh.harvard.edu]
Sent: Tuesday, June 30, 2015 10:55 PM
To: Morrissey, Stephen
Subject: FW: A question on process

Steve, How do we handle a correction like this? Thanks Mike

Michael F. Greene MD
Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Vincent Department of Obstetrics and Gynecology
Massachusetts General Hospital
Boston, MA 02114
(617)724-9014
greene.michael@mgh.harvard.edu

From: Mitchell, Allen A [mailto:allenmit@bu.edu]
Sent: Tuesday, June 30, 2015 12:09 PM
To: Greene, Michael Furman,M.D.
Cc: Louik, Carol
Subject: A question on process

Dear Michael,

Haven't been in touch, and hope all is going well. It would be great to catch up with you one of these days—maybe coffee?

I'm attaching a correction we wish to submit to the Journal—to whom would we send it? All authors of the original paper have agreed to sign the letter, though we didn't list them on the attached.

Interestingly, this was triggered by a colleague who's working for lawyers and has to earn his money, but the source of the prompt to re-look at the data is irrelevant. Let me know how we should proceed.

Warm regards,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
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From: Mitchell, Allen A
To: Reefhuis, Jennita (CDC/ONDIEH/NCBDDD); mrh7@cdc.gov; Tinker, Sarah (CDC/ONDIEH/NCBDDD)
Cc: Louik, Carol
Subject: FW: Participation request: Individual Patient Data meta-analysis on maternal depression, antidepressant use, and adverse pregnancy outcomes
Date: Tuesday, June 30, 2015 12:22:00 PM
Attachments: image001.png
image004.jpg
image003.jpg

Dear Jennita,

We thought you'd be interested in our reply to Marlene, however tardy it was.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
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allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Mitchell, Allen A
Sent: Tuesday, June 30, 2015 12:20 PM
To: 'Marleen.vanGelder@radboudumc.nl'
Cc: Richelle.Vlenterie@radboudumc.nl; Louik, Carol
Subject: RE: Participation request: Individual Patient Data meta-analysis on maternal depression, antidepressant use, and adverse pregnancy outcomes

Dear Marlene,

Please excuse the long delay in my reply, but we have been distracted by any number of "crises". I am afraid that, as much as we found your request intriguing, we simply don't have the financial or time resources that would be needed for us to participate in a way that we would consider appropriate.

Carol and I wish you the very best on this effort, and look forward to seeing you at the Boston ICPE.

Warm regards,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
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Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
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allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Marleen.vanGelder@radboudumc.nl [mailto:Marleen.vanGelder@radboudumc.nl]
Sent: Tuesday, April 28, 2015 4:39 AM
To: Mitchell, Allen A
Cc: Richelle.Vlenterie@radboudumc.nl; Louik, Carol
Subject: RE: Participation request: Individual Patient Data meta-analysis on maternal depression, antidepressant use, and adverse pregnancy outcomes

Dear Allen,

Thank you for your reply and my apologies for my late response. The analysis protocol (attached) got stuck at our legal department, which hampered me from officially answering your reasonable questions.

We included 202 papers, some of which were based on similar data sets (e.g., two paper using BDS data and three papers using NBDPS data). Most papers were on outcomes other than birth defects, although some small prospective studies also have some information available on this important outcome (but not the statistical power to analyze these data). For competitive considerations, we were initially not planning to share the bibliography in this phase of the study, but if necessary, we will send it to you as we know we can completely trust you on this. At this moment, Eurocat Northern Netherlands and MoBa agreed to participate, and we will be able to include data on birth defects from Hendrick et al. (2003). The NBDPS is also considering participation, but they had some additional questions as well. Unfortunately, we will not be able to include data from studies using the Scandinavian registries due to legislative issues and the Canadian TIS declined participation. We are awaiting some additional responses from other studies, some of which have not been contacted yet due to outdated contact information on the original paper.

In addition to the analysis protocol, I attached the data inventory file to give you a more detailed overview of the data we are requesting. For you, participation in this IPD meta-analysis would be to provide the raw data used for the publications (so published data only) on the variables of interest and to provide feedback on the draft paper. Regarding birth defects, we are requesting data on this outcome as specific as possible, as we are (of course) not going to lump them as one outcome. Studies that did so were excluded. I expect that we have to re-create categories, which will be based on the data we receive. The categorization will be done in cooperation with the respective researchers.

We are initially planning to write one paper for all outcomes, but if this gets too complicated, we will write separate papers on the different outcomes. For each paper, we will include authors from the

studies included in the respective paper. We do not have any conflicts of interest, but some participants may indeed have strong feelings about the safety of SSRIs and other antidepressants. We believe this may have been the case for some researchers who declined participation and this may be addressed in the Discussion section of the paper. Furthermore, we will share the preliminary results of the analyses among all participants and we hope that all collaborators will actively be involved in reviewing the draft paper(s).

Unfortunately, we are indeed not in position to provide financial support for participation in the IPD meta-analysis. We are aware of the time investment that comes with participation and therefore, we are trying to make it as easy as possible for you while providing you with opportunities to participate at the appropriate level (which may be different for every participant).

We hope this e-mail answers your questions. If you have any remaining questions or concerns, please do not hesitate to contact me.

Best,
Marleen

Marleen van Gelder, PhD
Assistant Professor
Department for Health Evidence & Radboud REshape Innovation Center
Radboud Institute for Health Sciences (RIHS)
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Geert Grooteplein Noord 21 (route 135)
www.radboudumc.nl/healthevidence | www.pridestudy.nl

Van: Mitchell, Allen A [mailto:allenmit@bu.edu]
Verzonden: Monday, March 23, 2015 5:23 PM
Aan: Gelder, Marleen van
CC: Vlenterie, Richelle; Louik, Carol
Onderwerp: RE: Participation request: Individual Patient Data meta-analysis on maternal depression, antidepressant use, and adverse pregnancy outcomes

Dear Marlene and Nel,

It was good to hear from you; I was not able to respond in the five days you proposed, but of course did want to get back to you.

In principle, it would be helpful to gain some clarity on the very disparate findings regarding risks of specific SSRIs in relation to specific birth defects. I do, however, have some questions for you, the

answers to which will help guide our decision.

It was unclear what our role might be (beyond co-authorship). This raises the question of just how you propose to proceed—from identifying studies for inclusion (how many of the 202 you identified dealt with birth defects?), to agreeing on the overall analytic plan. Were we to provide the kind of data you seek, it would be critical that we be fully satisfied that our data are analyzed appropriately. Further, how would you coordinate the many participants, some of whom have strong feelings about whether or not SSRIs are indeed associated with risks of birth defects?

We face another issue that is a bit of a catch-22: Were we to contribute data, we would need to be active participants at the appropriate level; however, for us to be active participants requires funding to support whoever might be doing that on our end. As a self-supporting research center, we are constrained in what we can provide (as you many know, we have recently had to decline offers to host students, despite our desire to take on such important activities). I suspect you are not in position to provide support, but thought it important to raise the concern.

I'm looking forward to hearing from you at your convenience.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
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allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Marleen.vanGelder@radboudumc.nl [mailto:Marleen.vanGelder@radboudumc.nl]
Sent: Monday, March 16, 2015 10:33 AM
To: Mitchell, Allen A
Cc: Richelle.Vlenterie@radboudumc.nl
Subject: Participation request: Individual Patient Data meta-analysis on maternal depression, antidepressant use, and adverse pregnancy outcomes

Dear Prof. Mitchell,

The prevalence of depression and the use of antidepressants during pregnancy have continued to increase over the last decades. Many published studies examined associations between depression and the use of antidepressants and adverse pregnancy outcomes, but the results remain inconsistent. This prompted us to design an Individual Patient Data (IPD) meta-analysis in which we would like to collaborate with you and authors of other studies on this topic.

Why an Individual Patient Data meta-analysis?

An IPD meta-analysis, i.e. a meta-analysis on the original individual data of previously published studies, offers the unique opportunity to analyze all available data on this topic simultaneously. Since IPD meta-analyses include more detailed data and contain larger numbers of subjects than single studies, they have much more statistical power to carry out informative subgroup analyses, e.g. on the timing of exposure to depression and the types of antidepressant used, and to thoroughly correct for confounding.

An IPD meta-analysis on the adverse effects of depression and antidepressant use during pregnancy.

In an ongoing systematic literature review, we indentified 202 published studies that are eligible to participate in the proposed IPD meta-analysis. The exposure assessments and outcome measurements varied across these studies, but we believe it is definitely worthwhile to try and conduct IPD meta-analyses of all cohort and case-control studies that examined the associations between depression and/or the use of antidepressants during pregnancy and selected adverse pregnancy outcomes (preterm birth, low birth weight, small for gestational age, low Apgar score, miscarriages, and specific birth defects).

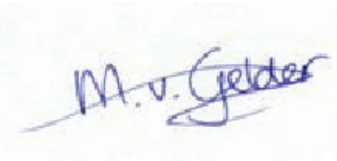
Therefore, we would like to invite you to participate in this IPD meta-analysis by providing access to (a part of) the raw dataset of the Pregnancy Health Interview Study (Birth Defects Study) as published by Louik et al. (2007 and 2014) and Toh et al. (2009) of which you are the principal investigator, as far as we know. If this is not the case, please forward this email to the person responsible for decisions about the above-mentioned data.

If you would be willing and able to collaborate in this IPD meta-analysis, we will draw up an official agreement in which we will arrange that:

- You will provide us with the necessary and available original data of your study for the purpose of the above-mentioned IPD meta-analysis.
- These data will remain the property of the principal investigators and will not be used for any other than the declared purpose.
- You are eligible for co-authorship on the meta-analysis paper, that will be written by Richelle Vlenterie and Marleen van Gelder as first and second author, unless you waive these rights.

We would be very grateful if you could reply about your willingness and ability to participate in the proposed IPD meta-analysis before March 20, 2015. We will then send you the agreement form, a data inventory file, and a preliminary analysis protocol.

Yours sincerely,



Dr. Marleen van Gelder,
Pharmacoepidemiologist

Dr. Nel Roeleveld
Reproductive Epidemiologist

Marleen van Gelder, PhD
Assistant Professor
Department for Health Evidence & Radboud REshape Innovation Center
Radboud Institute for Health Sciences (RIHS)
Marleen.vanGelder@radboudumc.nl
M +31 (0)6 17598562 / T +31 (0)24 3666126

Radboud university medical center
P.O.Box 9101, 6500 HB Nijmegen (HEV 133), The Netherlands
Geert Grooteplein Noord 21 (route 135)
www.radboudumc.nl/healthevidence | www.pridestudy.nl

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The Radboud university medical center is listed in the Commercial Register of the Chamber of Commerce under file number 41055629.

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The Radboud university medical center is listed in the Commercial Register of the Chamber of Commerce under file number 41055629.

From: Mitchell, Allen A
To: Solomon, Caren, M.D.; Galloway, Neil
Cc: Louik, Carol
Subject: RE:
Date: Wednesday, July 15, 2015 2:02:00 PM

I'll take any victory, however minor ;-)

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 15, 2015 1:51 PM
To: Mitchell, Allen A; Galloway, Neil
Cc: Louik, Carol
Subject: RE:

Good point. I suspect will change to neither of which was.. (will go through MS editor..)

From: Mitchell, Allen A [allenmit@bu.edu]
Sent: Wednesday, July 15, 2015 1:46 PM
To: Galloway, Neil
Cc: Solomon, Caren, M.D.; Louik, Carol
Subject: RE:

Dear Neil,
Thanks for the opportunity to review. All the changes look fine.

I do have one question that just came to notice—is the NEJM style to use the plural with "none of which" and "neither of which"? The original text (reflected in the last change noted) read "…none of which were common…", and the revised reads "…neither of which were common…". Just curious.

Many thanks again to both you and Caren.

Best,

Allen

(Please note new telephone number)

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Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Galloway, Neil [mailto:ngalloway@nejm.org]
Sent: Tuesday, July 14, 2015 4:52 PM
To: Mitchell, Allen A
Cc: Solomon, Caren, M.D.
Subject: RE:

Hi Allen,

Please see the attached correction form and let us know if this looks right, or if any further changes are needed.

Thanks and best regards,

Neil

From: Mitchell, Allen A [mailto:allenmit@bu.edu]
Sent: Monday, July 13, 2015 2:15 PM
To: Galloway, Neil; Solomon, Caren, M.D.
Subject: RE:

Thanks much!

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Galloway, Neil [mailto:ngalloway@nejm.org]
Sent: Monday, July 13, 2015 2:00 PM

To: Solomon, Caren, M.D.; Mitchell, Allen A
Subject: RE:

Will do. I can forward the correction notice to you both this afternoon.

Best regards,

Neil

From: Solomon, Caren, M.D.
Sent: Monday, July 13, 2015 1:38 PM
To: Mitchell, Allen A
Cc: Galloway, Neil
Subject: Re:

Neil- once we have correction ready to go, can you send to Allen to confirm ok? Thanks
On Jul 13, 2015, at 1:26 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

Thanks, Caren! Will we see the material before it's published?

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Monday, July 13, 2015 1:06 PM
To: Mitchell, Allen A
Cc: Galloway, Neil; Louik, Carol
Subject: Re:

Allan,
This sounds reasonable.Thanks again.
Will pass this right along.
Caren

On Jul 13, 2015, at 12:44 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

Dear Caren,

I had a chance to review the proposed revisions with Carol, and given the Journal's position on the value of p-values, we can accept virtually all the revisions you highlighted in bold. The only one of concern relates to the following :

Page 2680, first column, text beginning with "classification of heart defects…" The OR was stated here, but without any reference to the CI or statistical significance, so we think it can remain as is.
I see your point, but in sofar as other ORS that were higher than 2 but not statistically significant were not mentioned here, inclined to remove " a doubling of the risk of sepatal defects associated with sertraline use (OR2.0, based on 13 exposed subjects, and .."

First, we were pleased to see your statement that you were "inclined to remove…", leaving (we hope) an opportunity to convince you otherwise. You are correct that we did not mention other risks that were higher than 2-fold but not statistically significant, but we did indeed mention the one risk we observed in Tables 2 and 3 that had a lower bound of 1.0: On p. 2679, first column, "Exploratory Analyses", line 8, states " One association, that between paroxetine use and undescended testis, had a lower confidence bound of 1.0." Of interest, on page 2680, column 1, line 7, we noted that our "significant" finding for paroxetine and RVOTO was supported by a finding of borderline significance in the companion CDC report: "The latter finding is supported by an odds ratio of 2.5, based on seven exposed subjects (95% CI, 1.0 to 9.6), identified by Alwan et al in an article in this issue of the *Journal*." For reasons of consistency, then, we would ask that the text at the top of column 1, page 2680, be modified to the following (the modification in bold): "…we found a doubling of the risk of septal defects associated with sertraline use (odds ratio, 2.0**, lower confidence bound 1.0**), based on 13 exposed subjects…"

Please let me know what you think, and thank you very much for giving consideration to our perspectives.

Best,

Allen
(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Thursday, July 09, 2015 10:35 AM
To: Mitchell, Allen A; Galloway, Neil

Subject:

Allan-
We discussed as a group and feeling was that we needed to remove emphasis on findings that did not meet "formal" criteria for stat significance.. (to concord with usual reporting, but also because concerned about a lack of internal consistency if continue to highlight the sertraline risk, but then not other risks that appear elevated but not significant (eg LVOT obstruction with any SSRI..) .
See comments in bold below and let me know if you agree with these changes.
Once you let me know, we will pass along for correction.
Thanks again,
Caren

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 5:00 PM
To: Mitchell, Allen A
Subject: Re: RE:

Allan-
Of course I recognize that a lower bound of something like 0.97 would not really be too different from a lower bound of something like 1.02 , but strictly speaking one would be "significant" while other wouldn't per usual criteria. So useful to let me know the actual value that was rounded to 1.0. (even though again I appreciate that arbitrary distinction..)
Thanks again.

On Jul 1, 2015, at 3:47 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

> Dear Caren,
>
> Thanks for your note. We were not aware that the online version would be corrected, and of course we agree that all aspects of the text that make reference to the erroneous CI should be modified. Just to be clear, the lower bound changed from 1.2 to 1.0—the latter reflecting what many could call "borderline significance". Below are the sections of the text that mention or reflect the erroneous CI:
>
> **Abstract: Results, beginning with "Analyses of the associations…"** We seek guidance from you; as you know, we prefer to avoid the term "significant", but recognize this may not be a shared view. If you feel strongly that only "statistically significant" associations should be listed, **the portion of the sentence that includes "and septal defects (odds ratio, 2.0; 95% CI 1.0 to 4.0; 13 exposed subjects)" should be removed**; if you were comfortable replacing "significant associations" with "elevated risks", the reference to septal defects could remain, with the CI corrected.

Ms, page 2678, second column of text, last sentence: Again, we seek your guidance. The text beginning with "and two risk estimates had lower bounds that exceeded 1.0 .." could be changed to "…lower bounds of 1.0 or greater:" which would allow the sertraline estimate to remain**. Alternatively, if you wish to retain the "…lower bounds that exceeded 1.0:", the sertraline estimate would be removed and the preceding text would change from "…and two risk estimates.." to "and one risk estimate…"**

Page 2680, first column, text beginning with "classification of heart defects…" The OR was stated here, but without any reference to the CI or statistical significance, so we think it can remain as is.
I see your point, but in sofar as other ORS that were higher than 2 but not statistically significant were not mentioned here, inclined to remove " a doubling of the risk of sepatal defects associated with sertraline use (OR2.0, based on 13 exposed subjects, and .."

Second para, beginning with "Our observations…" Here we feel the word "significant" could be removed without changing the rest of the sentence, since the point we are trying to make is the variation in ORs, not necessarily whether they are "statistically significant".
Alternatively what about changing selected cardiac defects to "selected defects" (which then may refer also so omphalocele)?

Same page, second column, last line, beginning with "On the other hand…". This text remains **accurate if changed from "none of which" to "neither of which",**since paroxetine was "significantly" associated with right ventricular outflow tract obstruction and sertraline with omphalocele.

As you must know, we clearly regret this error, and appreciate your efforts in assuring that we set the record straight. We look forward to hearing back from you.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
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Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine

1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 12:11 PM
To: Mitchell, Allen A
Cc: Galloway, Neil; Morrissey, Stephen
Subject:

Dear Allen,
I hope you are doing well.
Mike forwarded your inquiry regarding a correction to your 2007 manuscript.
Unfortunately, making this correction will involve a few more changes than simply publishing the letter that you attached (I pasted below). To make sure the article is correct on line, we need to make change in each place in the article that the lower bound of the confidence interval was mentioned , and also need to change the associated interpretation (including in abstract) if this has changed (ie if the lower bound of "1.0" was actually slightly lower than 1 and thus no longer statistically significant using a 2 sided p value < 0.05?) Please send me a summary of all places (in order) where changes need to be made, and provide original wording/numbers and then wording/numbers that should replace.
Once you send this information, we can process correction.
Thank you in advance,

Caren

In response to an inquiry from a colleague regarding our paper "First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects" (NEJM ref), we discovered an error in Table 2. In that table, we reported an adjusted odds ratio for sertraline exposure in relation to septal defects as 2.0 with a 95% confidence interval of 1.2-4.0. On review of the original data tables, we confirmed that the odds ratio is correct as originally reported; however, due to a transcription error, the lower bound of the confidence interval should actually be 1.0 rather than 1.2. We have confirmed that all other entries in the table are correct as originally published.
We apologize for the error.

Sincerely,
Carol Louik etc.

entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

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From: Solomon, Caren, M.D.
To: Mitchell, Allen A
Subject: Re: RE: RE: RE:
Date: Wednesday, July 01, 2015 6:11:05 PM

I will defer any assessment of foolishness :-) Have a good trip.
Caren

On Jul 1, 2015, at 5:45 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

> Thanks, Caren. I'll be away next week, and will have only intermittent email contact. Is it foolish of me to remain hopeful that this example of a "distinction without a difference" will affect the Journal's thinking? I know the answer is "yes, it is foolish of me…", but I had to ask.
>
> Best,
>
> Allen
>
> **(Please note new telephone number)**
>
> Allen A. Mitchell, M.D.
> Director, Slone Epidemiology Center
> Professor of Epidemiology and Pediatrics
> Boston University Schools of Public Health and Medicine
> 1010 Commonwealth Avenue
> Boston, MA 02215
> allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119
>
> ---
>
> **From:** Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
> **Sent:** Wednesday, July 01, 2015 5:38 PM
> **To:** Mitchell, Allen A
> **Cc:** Galloway, Neil
> **Subject:** Re: RE: RE:
>
> Too bad..
> Let me chat with group re how best to correct. We won't have mtg until Tuesday owing to Friday holiday but will get back to you after that.
> Thanks again for information..
> Caren
>
> On Jul 1, 2015, at 5:13 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:
>
> > You said it, not me—0.97 is not really too different from 1.02. I'd go so far as to say "not different", and thus argues against making the distinction. But I won't win this, I know ;-). As it happens, our CI was 0.98 (not 1.0001, which would have made it "significant"). Now what?

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 5:00 PM
To: Mitchell, Allen A
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Thanks again.

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>
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> Abstract: Results, beginning with ‘’Analyses of the associations…” We seek guidance from you; as you know, we prefer to avoid the term “significant”, but recognize this may not be a shared view. If you feel strongly that only “statistically significant” associations should be listed, the portion of the sentence that includes “and septal defects (odds ratio, 2.0; 95% CI 1.0 to 4.0; 13 exposed subjects)” should be removed; if you were comfortable replacing

"significant associations" with "elevated risks", the reference to septal defects could remain, with the CI corrected.

Ms, page 2678, second column of text, last sentence: Again, we seek your guidance. The text beginning with "and two risk estimates had lower bounds that exceeded 1.0 .." could be changed to "…lower bounds of 1.0 or greater:" which would allow the sertraline estimate to remain.
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As you must know, we clearly regret this error, and appreciate your efforts in assuring that we set the record straight. We look forward to hearing back from you.

Best,

Allen

(Please note new telephone number)

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Dear Allen,
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Thank you in advance,

Caren

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We apologize for the error.

Sincerely,
Carol Louik etc.

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From: Louik, Carol
To: Mitchell, Allen A
Subject: RE:
Date: Thursday, July 09, 2015 11:19:07 AM

I'm not sure I totally understand the message, but I looked back at the paper to see if there were other associations that were "borderline significant" and how we dealt with it. There was one—an association between paroxetine and undescended testis, and in the results section, we did point that out so I think we should be allowed to do the same for the sertraline and septal defects. The LVOTO she mentions had a rounded lower bound of 0.9 so in her world that would not warrant mentioning (and the point estimate was only 1.6). So the only one of their suggestions I would take issue with is the one about removing the text about the point estimate of 2.0
Otherwise, I'm assuming the suggestions were all ours and they're just indicating how they would proceed. I don't have problem with the suggestion to change selected cardiac defects to selected defects.

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Mitchell, Allen A
Sent: Thursday, July 09, 2015 10:43 AM
To: Louik, Carol
Subject: Fwd:

Your thoughts? I haven't read it yet, but wanted to know your thinking before I respond on Monday. Oh--can you fwd me Sheila's email about the Monday call w BMS? In never got it.
Thanks,
Allen

Sent from my iPhone

Begin forwarded message:

> **From:** "Solomon, Caren, M.D." <csolomon@nejm.org>
> **Date:** July 9, 2015 at 10:35:13 AM EDT
> **To:** "'Mitchell, Allen A'" <allenmit@bu.edu>, "Galloway, Neil" <ngalloway@nejm.org>
>
> Allan-
> We discussed as a group and feeling was that we needed to remove emphasis on findings that did not meet "formal" criteria for stat significance.. (to concord with usual reporting, but also because concerned about a lack of internal consistency if continue to highlight the sertraline risk, but then not other risks that appear elevated but not significant (eg LVOT obstruction with any SSRI..) .

See comments in bold below and let me know if you agree with these changes.
Once you let me know, we will pass along for correction.
Thanks again,
Caren

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Sent: Wednesday, July 01, 2015 5:00 PM
To: Mitchell, Allen A
Subject: Re: RE:

Allan-
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Thanks again.

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> Thanks for your note. We were not aware that the online version would be corrected, and of course we agree that all aspects of the text that make reference to the erroneous CI should be modified. Just to be clear, the lower bound changed from 1.2 to 1.0—the latter reflecting what many could call “borderline significance”. Below are the sections of the text that mention or reflect the erroneous CI:
>
> **Abstract: Results, beginning with ‘’Analyses of the associations…”** We seek guidance from you; as you know, we prefer to avoid the term “significant”, but recognize this may not be a shared view. If you feel strongly that only “statistically significant” associations should be listed, **the portion of the sentence that includes “and septal defects (odds ratio, 2.0; 95% CI 1.0 to 4.0; 13 exposed subjects)” should be removed**; if you were comfortable replacing “significant associations” with “elevated risks”, the reference to septal defects could remain, with the CI corrected.
>
> **Ms, page 2678, second column of text, last sentence**:
> Again, we seek your guidance. The text beginning with “and two risk estimates had lower bounds that exceeded 1.0 ..”

could be changed to "…lower bounds of 1.0 or greater:" which would allow the sertraline estimate to remain**.**
Alternatively, if you wish to retain the "…lower bounds that exceeded 1.0:", the sertraline estimate would be removed and the preceding text would change from "… and two risk estimates.." to "and one risk estimate…"

Page 2680, first column, text beginning with "classification of heart defects…" The OR was stated here, but without any reference to the CI or statistical significance, so we think it can remain as is.
I see your point, but in sofar as other ORS that were higher than 2 but not statistically significant were not mentioned here, inclined to remove " a doubling of the risk of sepatal defects associated with sertraline use (OR2.0, based on 13 exposed subjects, and .."

Second para, beginning with "Our observations…" Here we feel the word "significant" could be removed without changing the rest of the sentence, since the point we are trying to make is the variation in ORs, not necessarily whether they are "statistically significant".
Alternatively what about changing selected cardiac defects to "selected defects" (which then may refer also so omphalocele)?

Same page, second column, last line, beginning with "On the other hand…". This text remains **accurate if changed from "none of which" to "neither of which",** since paroxetine was "significantly" associated with right ventricular outflow tract obstruction and sertraline with omphalocele.

As you must know, we clearly regret this error, and appreciate your efforts in assuring that we set the record straight. We look forward to hearing back from you.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.

Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 12:11 PM
To: Mitchell, Allen A
Cc: Galloway, Neil; Morrissey, Stephen
Subject:

Dear Allen,
I hope you are doing well.
Mike forwarded your inquiry regarding a correction to your 2007 manuscript.
Unfortunately, making this correction will involve a few more changes than simply publishing the letter that you attached (I pasted below). To make sure the article is correct on line, we need to make change in each place in the article that the lower bound of the confidence interval was mentioned , and also need to change the associated interpretation (including in abstract) if this has changed (ie if the lower bound of "1.0" was actually slightly lower than 1 and thus no longer statistically significant using a 2 sided p value < 0.05?) Please send me a summary of all places (in order) where changes need to be made, and provide original wording/numbers and then wording/numbers that should replace.
Once you send this information, we can process correction.
Thank you in advance,

Caren

In response to an inquiry from a colleague regarding our paper "First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects" (NEJM ref), we discovered an error in Table 2. In that table, we reported an adjusted odds ratio for sertraline exposure in relation to septal defects as 2.0 with a 95% confidence interval of 1.2-4.0. On review of the original data tables, we confirmed that the odds ratio is correct as originally reported; however, due to a transcription error, the lower bound of the confidence interval should actually be 1.0 rather than 1.2. We have confirmed that all other entries in the table are correct as originally published.

We apologize for the error.

Sincerely,
Carol Louik etc.

This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

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From: Louik, Carol
To: Mitchell, Allen A
Subject: RE: RE:
Date: Wednesday, July 01, 2015 5:06:58 PM

So what can you do? It was 0.98 Do we really have to call that different from 1.0? Don't people have bigger things to worry about?

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Mitchell, Allen A
Sent: Wednesday, July 01, 2015 5:03 PM
To: Louik, Carol
Subject: FW: RE:

Besides spelling my name wrong (!), she acknowledges the idiocy of calling a difference between 0.97 and 1.02—yet continues to use that cutoff!

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 5:00 PM
To: Mitchell, Allen A
Subject: Re: RE:

Allan-
Of course I recognize that a lower bound of something like 0.97 would not really be too different from a lower bound of something like 1.02 , but strictly speaking one would be "significant" while other wouldn't per usual criteria. So useful to let me know the actual value that was rounded to 1.0. (even though again I appreciate that arbitrary distinction..)
Thanks again.

On Jul 1, 2015, at 3:47 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

Dear Caren,

Thanks for your note. We were not aware that the online version would be corrected, and of course we agree that all aspects of the text that make reference to the erroneous CI should be modified. Just to be clear, the lower bound changed from 1.2 to 1.0—the latter reflecting what many could call "borderline significance". Below are the sections of the text that mention or reflect the erroneous CI:

Abstract: Results, beginning with ''Analyses of the associations…" We seek guidance from you; as you know, we prefer to avoid the term "significant", but recognize this may not be a shared view. If you feel strongly that only "statistically significant" associations should be listed, the portion of the sentence that includes "and septal defects (odds ratio, 2.0; 95% CI 1.0 to 4.0; 13 exposed subjects)" should be removed; if you were comfortable replacing "significant associations" with "elevated risks", the reference to septal defects could remain, with the CI corrected.

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Page 2680, first column, text beginning with "classification of heart defects…" The OR was stated here, but without any reference to the CI or statistical significance, so we think it can remain as is.

Second para, beginning with "Our observations…" Here we feel the word "significant" could be removed without changing the rest of the sentence, since the point we are trying to make is the variation in ORs, not necessarily whether they are "statistically significant".

Same page, second column, last line, beginning with "On the other hand…". This text remains accurate if changed from "none of which" to "neither of which", since paroxetine was "significantly" associated with right ventricular outflow tract obstruction and sertraline with omphalocele.

As you must know, we clearly regret this error, and appreciate your efforts in assuring that we set the record straight. We look forward to hearing back from you.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 12:11 PM
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Cc: Galloway, Neil; Morrissey, Stephen
Subject:

Dear Allen,
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Once you send this information, we can process correction.
Thank you in advance,

Caren

In response to an inquiry from a colleague regarding our paper "First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects" (NEJM ref), we discovered an error in Table 2. In that table, we reported an adjusted odds ratio for sertraline exposure in relation to septal defects as 2.0 with a 95% confidence interval of 1.2-4.0. On review of the original data tables, we confirmed that the odds ratio is correct as originally reported; however, due to a transcription error, the lower bound of the confidence interval should actually be 1.0 rather than 1.2. We have confirmed that all other entries in the table are correct as originally published.
We apologize for the error.

Sincerely,
Carol Louik etc.

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From: Mitchell, Allen A
To: Nicholas P. JEWELL
Cc: Louik, Carol
Subject: RE: Louik et al (NEJM, 2007)
Date: Monday, July 13, 2015 2:27:00 PM

Dear Dr. Jewell,

Thanks for your inquiry. Dr. Kimmel brought to our attention a potential error in one of our confidence bounds that we published in the NEJM. There was indeed an error, and we have submitted a correction to the Journal. Our efforts were solely directed at assuring that what we published was correct; we are not involved in the litigation in any way and as a matter of policy we allow our publications to speak for themselves.

Sincerely,

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Nicholas P. JEWELL [mailto:jewell@berkeley.edu]
Sent: Tuesday, July 07, 2015 1:15 PM
To: Mitchell, Allen A
Subject: Louik et al (NEJM, 2007)

Dear Dr. Mitchell:

I received an email between you and Dr Stephen Kimmel (dated July 1 2015, I believe) that was relied upon in an expert report he just filed in the Zoloft litigation. I would be very interested in seeing the printout of the statistical analysis (a logistic regression model I assume) that yielded this revised odds ratio estimate and confidence interval. Can you possibly send me the underlying logistic regression output. (I am Professor of Biostatistics & Statistics at the University of California, Berkeley.)

Thanks!

Nicholas P. Jewell

From: Louik, Carol
To: Mitchell, Allen A
Subject: FW: correction to
Date: Thursday, July 09, 2015 4:16:31 PM

I realized after I wrote this that you might be irritated by my pointing out that you were senior author. I didn't mean anything by it; it just seemed to me that I had to have some excuse for not responding myself. Sorry if it was the wrong thing to do.

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Louik, Carol
Sent: Thursday, July 09, 2015 3:53 PM
To: 'Sander Greenland'; Hernandez-Diaz, Sonia; Werler, Martha M; Angela Lin
Cc: Mitchell, Allen A
Subject: RE: correction to

Dear Sander

As you know, Dr. Mitchell is out of the office this week, but will be returning on Monday, July 13. As he is senior author of this paper, he will respond to you when he returns.

Best,

Carol

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Thursday, July 09, 2015 11:50 AM
To: Hernandez-Diaz, Sonia; Werler, Martha M; Louik, Carol
Subject: Re: correction to

Hi Sonia (and Martha and Carol),

Take a look at the exhibit 82 I sent - as you can see the defense expert obtained the results from Alan on request, and used them to place enormous stock in their "nonsignficance" and the confidence interval excluding or including 1. The e-mail exchange with Alan follows the exxpert's statement to the court.

Statisticians and epidemiologists freely present opinions in these legal documents that pander to the testing fetish even though they wouldn't dare do that in one of our journals (and wouldn't even be allowed to in Epidemiology), and the Supreme Court itself has rejected that standard (see last attachment). Still, the judge in this case puts great stock in the magic 0.05 so I am copying this material to Carol.

Carol, I would be very grateful if you could supply the additional digit to the sertraline-septal defect.

With best wishes and thanks in advance,

Sander

On 7/9/2015 1:42 AM, Hernandez-Diaz, Sonia wrote:

> Dear Sander,
> Carol Louik run the analyses and provided the estimates. I do not know the decimal points.
>
> I understand this is important for the lawyers and that numbers should be accurate. However, I hope the decision to whether consider Sertraline guilty or not is not based on a decimal point from one observational study. Please see the BMJ publication from today concluding there are no increased risks associated with Sertraline.
> This topic is the Cape Horn of epidemiologic (conflicting) evidence, I am so glad you are involved in the discussion.
>
> All the best,
> Sonia
>
> ---
>
> **From:** Sander Greenland [mailto:lesdomes@g.ucla.edu]
> **Sent:** Wednesday, July 08, 2015 4:02 PM
> **To:** Hernandez-Diaz, Sonia; Werler, Martha M
> **Subject:** correction to
>
> Dear Sonia and Martha,
>
> Sorry to bother you with this request, but I got a call from a plaintiff lawyer (Mark Robinson) who consults me on occasion, this time on in a case involving sertraline and septal defects. I'm told I am not a named expert in this case, but he wanted to know if the statistical significance

changed due to the correction to the odds-ratio estimate of 2.0 (1.2, 4.0) highlighted in Table 2 of the attached 2007 article on which you are coauthors.

The defense expert, Steve Kimmel, had contacted Alan Mitchell last month about it and got back the correction shown in the attached e-mail exchange.

Alan supplied the defense expert with the correction showing 2.0 (1.0,4.0). Unsurprisingly, the big question it has raised is what are the results to two digits past the decimal point, particularly what is the lower limit out to one more digit?
Alan said in the e-mails to Kimmel that he would be consulting with his coauthors, so I am writing to ask if either of you can state the estimate in more detail?

Again, apologies for bothering you with this request, but I was told Alan is away right now, and I am curious myself about the answer given the capital that Kimmel seems to have made of it (as you can see in the attached exhibit).
I hope it is an easy question to answer given that Alan mentioned having retrieved the original files in his response to Kimmel.

Thanking you in advance,
All the Best,
Sander

From: Louik, Carol
To: Mitchell, Allen A
Subject: RE: correction to
Date: Thursday, July 09, 2015 2:34:02 PM

I know you're not dealing with this now, which is fine, but just so you know, when you do, the lower bound is 0.982, which does round up to 1.0, and in my opinion, anyone who cares that much about the second decimal place doesn't really understand the nature of observational studies. Just my opinion.

Carol Louik, Sc.D.
Assistant Professor
Slone Epidemiology Center at Boston University
1010 Commonwealth Ave.
Boston, MA 02215
phone: 617-206-6208
fax: 617-738-5119

-----Original Message-----
From: Mitchell, Allen A
Sent: Thursday, July 09, 2015 1:31 PM
To: Louik, Carol
Subject: Re: correction to

Right!

Sent from my iPhone

> On Jul 9, 2015, at 11:53 AM, Louik, Carol <clouik@bu.edu> wrote:
>
> This message cannot be displayed because of the way it is formatted. Ask the sender to send it again using a different format or email program. message/rfc822

From: Lin, Angela E.,M.D.
To: Louik, Carol; Hernandez-Diaz, Sonia; Werler, Martha M
Cc: Mitchell, Allen A
Subject: do not forward
Date: Thursday, July 09, 2015 4:11:10 PM

[thank you VERY much for sharing, I wondered what was going on behind the scene. Are they serious?]

From: Louik, Carol [clouik@bu.edu]
Sent: Thursday, July 09, 2015 3:52 PM
To: Sander Greenland; Hernandez-Diaz, Sonia; Werler, Martha M; Lin, Angela E.,M.D.
Cc: Mitchell, Allen A
Subject: RE: correction to

Dear Sander

As you know, Dr. Mitchell is out of the office this week, but will be returning on Monday, July 13. As he is senior author of this paper, he will respond to you when he returns.

Best,

Carol

Carol Louik, Sc.D.
Assistant Professor
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> I understand this is important for the lawyers and that numbers should be accurate. However, I hope the decision to whether consider Sertraline guilty or not is not based on a decimal point from one observational study. Please see the BMJ publication from today concluding there are no increased risks associated with Sertraline.
> This topic is the Cape Horn of epidemiologic (conflicting) evidence, I am so glad you are involved in the discussion.
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> All the best,
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> Dear Sonia and Martha,
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>
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>
> Alan supplied the defense expert with the correction showing 2.0

(1.0,4.0). Unsurprisingly, the big question it has raised is what are the results to two digits past the decimal point, particularly what is the lower limit out to one more digit?
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I hope it is an easy question to answer given that Alan mentioned having retrieved the original files in his response to Kimmel.

Thanking you in advance,
All the Best,
Sander

EXHIBIT 82

SUPPLEMENT TO REPORT FOR ZOLOFT FEDERAL LITIGATION

Supplement to Expert Report of Stephen E. Kimmel, MD, MSCE, FACC, FAHA, FISPE

I am submitting this supplement to my report in connection with litigation regarding whether Zoloft (sertraline), an antidepressant medication manufactured by Pfizer, can cause congenital heart defects. This supplement discusses an important update to the results of Louik et al. and the results of a new peer-reviewed, published meta-analysis.

Louik et al. (*New England Journal of Medicine*, 2007) was one of only 2 independent studies that reported a statistically significantly increased risk of overall septal defects among Zoloft exposed women. The odds ratio and 95% confidence interval in the published paper was 2.0 (95% confidence interval [CI] 1.2–4.0). Because the lower bound of the confidence interval excluded 1.0, the results were statistically significant. As I further reviewed the studies addressing Zoloft and cardiac defects, I noticed that the confidence interval around the odds ratio was not symmetric on the log scale (it should be symmetric). Because of this, I contacted Allen Mitchell, the senior author of the paper, and inquired if the published results were accurate. On July 1, 2015, Dr. Mitchell replied: "As it happens, we were able to retrieve the original files for the paper, and we did indeed err in transcribing the CI for the adjusted odds ratio for sertraline exposure in relation to septal defects (all of the other values in that table were correct). The point estimate (2.0) was correct, but the published CI of 1.2-4.0 should have been 1.0-4.0. We have notified the NEJM of the error, and they will publish a correction along with a corrected online version of the ms [manuscript] that reflects the change in CIs. Thanks for bringing this matter to our attention." With these corrected results, Louik no longer demonstrates a confidence interval that excludes one. As such, the results of Louik can not be considered as independent, statistically significant validation of the only independent finding of a statistically significant relationship between Zoloft and septal defects (Jimenez-Solem et al.). Further, as I noted in my second MDL report, the Jimenez-Solem study was designed "to try to address the

lingering concerns about uncontrolled confounding in these [other Danish] studies" and concluded that "that risks related to SSRI use during the first trimester are a result of an unaccounted confounder…."

The new study that was published after my report was prepared, Wang et al., is a meta-analysis of SSRIs and cardiac defects published in the *Journal of the American Heart Association*. The odds ratio for cardiac defects and Zoloft in this study was 1.00 (95% confidence interval of 0.81 to 1.20). This meta-analysis used a different study selection process from the other 2 published meta-analysis but came to the same conclusion that "SSRIs during the first trimester in pregnant women were not associated with increased risks for newborn heart defects."

Thus, the correct results from Louik et al. and the results from the newly published meta-analysis provide yet additional support for the conclusion that Zoloft does not cause cardiac birth defects.

Dated: July 2, 2015

Stephen E. Kimmel, MD, MSCE, FACC, FAHA, FISPE

Attachment

Dear Steve,

As you might imagine, the timing of our response cannot be driven by your court-related work. As it happens, we were able to retrieve the original files for the paper, and we did indeed err in transcribing the CI for the adjusted odds ratio for sertraline exposure in relation to septal defects (all of the other values in that table were correct). The point estimate (2.0) was correct, but the published CI of 1.2-4.0 should have been 1.0-4.0. We have notified the NEJM of the error, and they will publish a correction along with a corrected online version of the ms that reflects the change in CIs. Thanks for bringing this matter to our attention.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Stephen Kimmel [mailto:stevek@mail.med.upenn.edu]
Sent: Wednesday, July 01, 2015 11:23 AM
To: Mitchell, Allen A
Subject: Re: Question about NEJM paper

Hi Allen,

Just wanted to check back on this. There is a court-imposed deadline of this coming Tuesday and I will likely be asked about this in court. If there is any way to get some clarification on this issue before then, I would greatly appreciate it. I am also happy to work with Carol directly on this.

Thanks.

Sorry, Steve, for not responding more promptly. Your note came at a particularly busy time, and I have not yet had a chance to discuss your request with Carol. I will get back to you when that has happened. Hope to see you in Boston in August.
Sent from my iPhone

On Jun 22, 2015, at 8:19 PM, Stephen Kimmel <stevek@mail.med.upenn.edu> wrote:

Re: Question about NEJM paper Hi Allen, just wanted to check to see if you got this email and to see if you might have some insights on this. I realize this is an older study and that it may be hard to clarify. Let me know what you think is possible if you can. Thanks.

Tuesday, June 16, 2015, 11:07:05 PM, you wrote:

Hi Allen, how are you? I am writing to ask you a question about your 2007 NEJM paper on SSRIs and birth defects. By way of disclosure, I have been serving as a consultant in litigation surrounding sertraline and birth defects.

My question relates to the OR and CI for sertraline and septal defects in Table 2 of the paper: 2.0 (1.2-4.0). When I plot this on a log scale, the CI is not symmetric. Also, the OR seems a bit high given the prevalence of exposure in the sertraline group.

Can you help me to clarify the results for sertraline and septal defects so I am clear that I have the correct numbers?

Thanks. Hope all is well.

-Steve

--
Stephen Kimmel, MD, MSCE
Professor of Medicine and Epidemiology
Director, Division of Epidemiology
Director, Center for Therapeutic Effectiveness Research
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA 19104-6021
stevek@mail.med.upenn.edu

--
- Steve

- Steve

Syllabus

NOTE: Where it is feasible, a syllabus (headnote) will be released, as is being done in connection with this case, at the time the opinion is issued. The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States* v. *Detroit Timber & Lumber Co.*, 200 U. S. 321, 337.

SUPREME COURT OF THE UNITED STATES

Syllabus

MATRIXX INITIATIVES, INC., ET AL. *v.* SIRACUSANO ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

No. 09–1156. Argued January 10, 2011—Decided March 22, 2011

Respondents filed this securities fraud class action, alleging that petitioners (hereinafter Matrixx) violated §10(b) of the Securities Exchange Act of 1934 and Securities and Exchange Commission Rule 10b–5 by failing to disclose reports of a possible link between Matrixx's leading product, Zicam Cold Remedy, and loss of smell (anosmia), rendering statements made by Matrixx misleading. Matrixx moved to dismiss the complaint, arguing that respondents had not pleaded the element of a material misstatement or omission and the element of scienter. The District Court granted the motion, but the Ninth Circuit reversed. It held that the District Court erred in requiring an allegation of statistical significance to establish materiality, concluding instead that the complaint adequately alleged information linking Zicam and anosmia that would have been significant to a reasonable investor. It also held that Matrixx's withholding of information about reports of adverse effects and about pending lawsuits by Zicam users gave rise to a strong inference of scienter.

Held: Respondents have stated a claim under §10(b) and Rule 10b–5. Pp. 8–22.

(a) To prevail on their claim, respondents must prove, as relevant here, a material misrepresentation or omission by Matrixx and scienter. See *Stoneridge Investment Partners, LLC* v. *Scientific-Atlanta, Inc.*, 552 U. S. 148, 157. Matrixx contends that they failed to plead these required elements because they did not allege that the reports Matrixx received reflected statistically significant evidence that Zicam caused anosmia. Pp. 8–9.

(b) Respondents have adequately pleaded materiality. Pp. 9–19.

(1) Under *Basic Inc.* v. *Levinson*, 485 U. S. 224, §10(b)'s material-

ity requirement is satisfied when there is " 'a substantial likelihood that the disclosure of the omitted fact would have been viewed by the reasonable investor as having significantly altered the "total mix" of information made available.' " *Id.*, at 231–232. The Court declined to adopt a bright-line rule for determining materiality in *Basic*, observing that "[a]ny approach that designates a single fact or occurrence as always determinative of an inherently fact-specific finding such as materiality, must necessarily be overinclusive or underinclusive." *Id.*, at 236. Here, Matrixx's bright-line rule—that adverse event reports regarding a pharmaceutical company's products are not material absent a sufficient number of such reports to establish a statistically significant risk that the product is causing the events—would "artificially exclud[e]" information that "would otherwise be considered significant to [a reasonable investor's] trading decision." *Ibid.* Matrixx's premise that statistical significance is the only reliable indication of causation is flawed. Both medical experts and the Food and Drug Administration rely on evidence other than statistically significant data to establish an inference of causation. It thus stands to reason that reasonable investors would act on such evidence. Because adverse reports can take many forms, assessing their materiality is a fact-specific inquiry, requiring consideration of their source, content, and context. The question is whether a *reasonable* investor would have viewed the nondisclosed information " 'as having significantly altered the "total mix" of information made available.' " *Id.,* at 232. Something more than the mere existence of adverse event reports is needed to satisfy that standard, but that something more is not limited to statistical significance and can come from the source, content, and context of the reports. Pp. 9–16.

(2) Applying *Basic*'s "total mix" standard here, respondents adequately pleaded materiality. The complaint's allegations suffice to "raise a reasonable expectation that discovery will reveal evidence" satisfying the materiality requirement, *Bell Atlantic Corp.* v. *Twombly*, 550 U. S. 544, 556, and to "allo[w] the court to draw the reasonable inference that the defendant is liable," *Ashcroft* v. *Iqbal*, 556 U. S. ___, ___. Assuming the complaint's allegations to be true, Matrixx received reports from medical experts and researchers that plausibly indicated a reliable causal link between Zicam and anosmia. Consumers likely would have viewed Zicam's risk as substantially outweighing its benefit. Viewing the complaint's allegations as a whole, the complaint alleges facts suggesting a significant risk to the commercial viability of Matrixx's leading product. It is substantially likely that a reasonable investor would have viewed this information " 'as having significantly altered the "total mix" of information made available.' " *Basic*, *supra,* at 232. Assuming the

Syllabus

complaint's allegations to be true, Matrixx told the market that revenues were going to rise 50 and then 80 percent when it had information indicating a significant risk to its leading revenue-generating product. It also publicly dismissed reports linking Zicam and anosmia and stated that zinc gluconate's safety was well established, when it had evidence of a biological link between Zicam's key ingredient and anosmia and had conducted no studies to disprove that link. Pp. 16–19.

(c) Respondents have also adequately pleaded scienter, " 'a mental state embracing intent to deceive, manipulate, or defraud,' " *Tellabs, Inc.* v. *Makor Issues & Rights, Ltd.*, 551 U. S. 308, 319. This Court assumes, without deciding, that the scienter requirement may be satisfied by a showing of deliberate recklessness. Under the Private Securities Litigation Reform Act of 1995, a complaint adequately pleads scienter "only if a reasonable person would deem the inference of scienter cogent and at least as compelling as any opposing inference one could draw from the facts alleged." *Id.*, at 324. Matrixx's proposed bright-line rule requiring an allegation of statistical significance to establish a strong inference of scienter is once again flawed. The complaint's allegations, "taken collectively," give rise to a "cogent and compelling" inference that Matrixx elected not to disclose adverse event reports not because it believed they were meaningless but because it understood their likely effect on the market. *Id.,* at 323, 324. "[A] reasonable person" would deem the inference that Matrixx acted with deliberate recklessness "at least as compelling as any [plausible] opposing inference." *Id.*, at 324. Pp. 19–22.

585 F. 3d 1167, affirmed.

SOTOMAYOR, J., delivered the opinion for a unanimous Court.

SUPREME COURT OF THE UNITED STATES

No. 09–1156

MATRIXX INITIATIVES, INC., ET AL., PETITIONERS *v.* JAMES SIRACUSANO ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

[March 22, 2011]

JUSTICE SOTOMAYOR delivered the opinion of the Court.

This case presents the question whether a plaintiff can state a claim for securities fraud under §10(b) of the Securities Exchange Act of 1934, 48 Stat. 891, as amended, 15 U. S. C. §78j(b), and Securities and Exchange Commission (SEC) Rule 10b–5, 17 CFR §240.10b–5 (2010), based on a pharmaceutical company's failure to disclose reports of adverse events associated with a product if the reports do not disclose a statistically significant number of adverse events. Respondents, plaintiffs in a securities fraud class action, allege that petitioners, Matrixx Initiatives, Inc., and three of its executives (collectively Matrixx), failed to disclose reports of a possible link between its leading product, a cold remedy, and loss of smell, rendering statements made by Matrixx misleading. Matrixx contends that respondents' complaint does not adequately allege that Matrixx made a material representation or omission or that it acted with scienter because the complaint does not allege that Matrixx knew of a statistically significant number of adverse events requiring disclosure. We conclude that the materiality of adverse event reports cannot

be reduced to a bright-line rule. Although in many cases reasonable investors would not consider reports of adverse events to be material information, respondents have alleged facts plausibly suggesting that reasonable investors would have viewed these particular reports as material. Respondents have also alleged facts "giving rise to a strong inference" that Matrixx "acted with the required state of mind." 15 U. S. C. A. §78u–4(b)(2)(A) (Feb. 2011 Supp.). We therefore hold, in agreement with the Court of Appeals for the Ninth Circuit, that respondents have stated a claim under §10(b) and Rule 10b–5.

I

A

Through a wholly owned subsidiary, Matrixx develops, manufactures, and markets over-the-counter pharmaceutical products. Its core brand of products is called Zicam. All of the products sold under the name Zicam are used to treat the common cold and associated symptoms. At the time of the events in question, one of Matrixx's products was Zicam Cold Remedy, which came in several forms including nasal spray and gel. The active ingredient in Zicam Cold Remedy was zinc gluconate. Respondents allege that Zicam Cold Remedy accounted for approximately 70 percent of Matrixx's sales.

Respondents initiated this securities fraud class action against Matrixx on behalf of individuals who purchased Matrixx securities between October 22, 2003, and February 6, 2004.[1] The action principally arises out of statements that Matrixx made during the class period relating to revenues and product safety. Respondents claim that Matrixx's statements were misleading in light of reports that Matrixx had received, but did not disclose, about

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[1] According to the complaint, Matrixx securities were traded on the NASDAQ National Market. App. 99a.

consumers who had lost their sense of smell (a condition called anosmia) after using Zicam Cold Remedy. Respondents' consolidated amended complaint alleges the following facts, which the courts below properly assumed to be true. See *Ashcroft* v. *Iqbal*, 556 U. S. ___, ___ (2009) (slip op., at 14).

In 1999, Dr. Alan Hirsch, neurological director of the Smell & Taste Treatment and Research Foundation, Ltd., called Matrixx's customer service line after discovering a possible link between Zicam nasal gel and a loss of smell "in a cluster of his patients." App. 67a–68a. Dr. Hirsch told a Matrixx employee that "previous studies had demonstrated that intranasal application of zinc could be problematic." *Id.*, at 68a. He also told the employee about at least one of his patients who did not have a cold and who developed anosmia after using Zicam.

In September 2002, Timothy Clarot, Matrixx's vice president for research and development, called Miriam Linschoten, Ph.D., at the University of Colorado Health Sciences Center after receiving a complaint from a person Linschoten was treating who had lost her sense of smell after using Zicam. Clarot informed Linschoten that Matrixx had received similar complaints from other customers. Linschoten drew Clarot's attention to "previous studies linking zinc sulfate to loss of smell." *Ibid.* Clarot gave her the impression that he had not heard of the studies. She asked Clarot whether Matrixx had done any studies of its own; he responded that it had not but that it had hired a consultant to review the product. Soon thereafter, Linschoten sent Clarot abstracts of the studies she had mentioned. Research from the 1930's and 1980's had confirmed "[z]inc's toxicity." *Id.*, at 69a. Clarot called Linschoten to ask whether she would be willing to participate in animal studies that Matrixx was planning, but she declined because her focus was human research.

By September 2003, one of Linschoten's colleagues at

the University of Colorado, Dr. Bruce Jafek, had observed 10 patients suffering from anosmia after Zicam use. Linschoten and Jafek planned to present their findings at a meeting of the American Rhinologic Society in a poster presentation entitled "Zicam® Induced Anosmia." *Ibid.* (internal quotation marks omitted). The American Rhinologic Society posted their abstract in advance of the meeting. The presentation described in detail a 55-year-old man with previously normal taste and smell who experienced severe burning in his nose, followed immediately by a loss of smell, after using Zicam. It also reported 10 other Zicam users with similar symptoms.

Matrixx learned of the doctors' planned presentation. Clarot sent a letter to Dr. Jafek warning him that he did not have permission to use Matrixx's name or the names of its products. Dr. Jafek deleted the references to Zicam in the poster before presenting it to the American Rhinologic Society.

The following month, two plaintiffs commenced a product liability lawsuit against Matrixx alleging that Zicam had damaged their sense of smell. By the end of the class period on February 6, 2004, nine plaintiffs had filed four lawsuits.

Respondents allege that Matrixx made a series of public statements that were misleading in light of the foregoing information. In October 2003, after they had learned of Dr. Jafek's study and after Dr. Jafek had presented his findings to the American Rhinologic Society, Matrixx stated that Zicam was "'poised for growth in the upcoming cough and cold season'" and that the company had "'very strong momentum.'"[2] *Id.*, at 72a–74a. Matrixx further

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[2] At oral argument, counsel for the United States, which submitted an *amicus curiae* brief in support of respondents, suggested that some of these statements might qualify as nonactionable "puffery." Tr. of Oral Arg. 51–52. This question is not before us, as Matrixx has not advanced such an argument.

expressed its expectation that revenues would "'be up in excess of 50% and that earnings, per share for the full year [would] be in the 25 to 30 cent range.'" *Id.*, at 74a. In January 2004, Matrixx raised its revenue guidance, predicting an increase in revenues of 80 percent and earnings per share in the 33-to-38-cent range.

In its Form 10–Q filed with the SEC in November 2003, Zicam warned of the potential "'material adverse effect'" that could result from product liability claims, "'whether or not proven to be valid.'" *Id.*, at 75a–76a. It stated that product liability actions could materially affect Matrixx's "'product branding and goodwill,'" leading to reduced customer acceptance.[3] *Id.*, at 76a. It did not disclose, however, that two plaintiffs had already sued Matrixx for allegedly causing them to lose their sense of smell.

On January 30, 2004, Dow Jones Newswires reported that the Food and Drug Administration (FDA) was "'looking into complaints that an over-the-counter common-cold medicine manufactured by a unit of Matrixx Initiatives, Inc. (MTXX) may be causing some users to lose their sense of smell'" in light of at least three product liability lawsuits. *Id.*, at 79a–80a. Matrixx's stock fell from $13.55 to $11.97 per share after the report. In response, on February 2, Matrixx issued a press release that stated:

> "All Zicam products are manufactured and marketed according to FDA guidelines for homeopathic medicine. Our primary concern is the health and safety of our customers and the distribution of factual information about our products. Matrixx believes statements alleging that intranasal Zicam products caused anosmia (loss of smell) are completely un-

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[3] Respondents also allege that Matrixx falsely reported its financial results in the Form 10–Q by failing to reserve for or disclose potential liability, in violation of Generally Accepted Accounting Principles. The Court of Appeals did not rely on these allegations.

> founded and misleading.
>
> "In no clinical trial of intranasal zinc gluconate gel products has there been a single report of lost or diminished olfactory function (sense of smell). Rather, the safety and efficacy of zinc gluconate for the treatment of symptoms related to the common cold have been well established in two double-blind, placebo-controlled, randomized clinical trials. In fact, in neither study were there any reports of anosmia related to the use of this compound. The overall incidence of adverse events associated with zinc gluconate was extremely low, with no statistically significant difference between the adverse event rates for the treated and placebo subsets.
>
> "A multitude of environmental and biologic influences are known to affect the sense of smell. Chief among them is the common cold. As a result, the population most likely to use cold remedy products is already at increased risk of developing anosmia. Other common causes of olfactory dysfunction include age, nasal and sinus infections, head trauma, anatomical obstructions, and environmental irritants." *Id.*, at 77a–78a (internal quotation marks omitted).

The day after Matrixx issued this press release, its stock price bounced back to $13.40 per share.

On February 6, 2004, the end of the class period, Good Morning America, a nationally broadcast morning news program, highlighted Dr. Jafek's findings. (The complaint does not allege that Matrixx learned of the news story before its broadcast.) The program reported that Dr. Jafek had discovered more than a dozen patients suffering from anosmia after using Zicam. It also noted that four lawsuits had been filed against Matrixx. The price of Matrixx stock plummeted to $9.94 per share that same day. Zicam again issued a press release largely repeating its February

2 statement.

On February 19, 2004, Matrixx filed a Form 8–K with the SEC stating that it had "'convened a two-day meeting of physicians and scientists to review current information on smell disorders'" in response to Dr. Jafek's presentation. *Id.*, at 82a. According to the Form 8–K, "'In the opinion of the panel, there is insufficient scientific evidence at this time to determine if zinc gluconate, when used as recommended, affects a person's ability to smell.'" *Ibid.* A few weeks later, a reporter quoted Matrixx as stating that it would begin conducting "'animal and human studies to further characterize these post-marketing complaints.'" *Id.*, at 84a.

On the basis of these allegations, respondents claimed that Matrixx violated §10(b) of the Securities Exchange Act and SEC Rule 10b–5 by making untrue statements of fact and failing to disclose material facts necessary to make the statements not misleading in an effort to maintain artificially high prices for Matrixx securities.

B

Matrixx moved to dismiss respondents' complaint, arguing that they had failed to plead the elements of a material misstatement or omission and scienter. The District Court granted the motion to dismiss. Relying on *In re Carter-Wallace, Inc., Securities Litigation*, 220 F. 3d 36 (CA2 2000), it held that respondents had not alleged a "statistically significant correlation between the use of Zicam and anosmia so as to make failure to public[ly] disclose complaints and the University of Colorado study a material omission." App. to Pet. for Cert. 50a. The District Court similarly agreed that respondents had not stated with particularity facts giving rise to a strong inference of scienter. See 15 U. S. C. A. §78u–4(b)(2)(A) (Feb. 2011 Supp.). It noted that the complaint failed to allege that Matrixx disbelieved its statements about Zi-

cam's safety or that any of the defendants profited or attempted to profit from Matrixx's public statements. App. to Pet. for Cert. 52a.

The Court of Appeals reversed. 585 F. 3d 1167 (CA9 2009). Noting that "'[t]he determination [of materiality] requires delicate assessments of the inferences a "reasonable shareholder" would draw from a given set of facts and the significance of those inferences to him,'" *id.*, at 1178 (quoting *Basic Inc.* v. *Levinson*, 485 U. S. 224, 236 (1988); some internal quotation marks omitted; alterations in original), the Court of Appeals held that the District Court had erred in requiring an allegation of statistical significance to establish materiality. It concluded, to the contrary, that the complaint adequately alleged "information regarding the possible link between Zicam and anosmia" that would have been significant to a reasonable investor. 585 F. 3d, at 1179, 1180. Turning to scienter, the Court of Appeals concluded that "[w]ithholding reports of adverse effects of and lawsuits concerning the product responsible for the company's remarkable sales increase is 'an extreme departure from the standards of ordinary care,'" giving rise to a strong inference of scienter. *Id.*, at 1183.

We granted certiorari, 560 U. S. ___ (2010), and we now affirm.

II

Section 10(b) of the Securities Exchange Act makes it unlawful for any person to "use or employ, in connection with the purchase or sale of any security . . . any manipulative or deceptive device or contrivance in contravention of such rules and regulations as the Commission may prescribe as necessary or appropriate in the public interest or for the protection of investors." 15 U. S. C. §78j(b). SEC Rule 10b–5 implements this provision by making it unlawful to, among other things, "make any untrue statement of a material fact or to omit to state a material

fact necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading." 17 CFR §240.10b–5(b). We have implied a private cause of action from the text and purpose of §10(b). See *Tellabs, Inc.* v. *Makor Issues & Rights, Ltd.*, 551 U. S. 308, 318 (2007).

To prevail on their claim that Matrixx made material misrepresentations or omissions in violation of §10(b) and Rule 10b–5, respondents must prove "(1) a material misrepresentation or omission by the defendant; (2) scienter; (3) a connection between the misrepresentation or omission and the purchase or sale of a security; (4) reliance upon the misrepresentation or omission; (5) economic loss; and (6) loss causation." *Stoneridge Investment Partners, LLC* v. *Scientific-Atlanta, Inc.*, 552 U. S. 148, 157 (2008). Matrixx contends that respondents have failed to plead both the element of a material misrepresentation or omission and the element of scienter because they have not alleged that the reports received by Matrixx reflected statistically significant evidence that Zicam caused anosmia. We disagree.

A

We first consider Matrixx's argument that "adverse event reports that do not reveal a statistically significant increased risk of adverse events from product use are not material information." Brief for Petitioners 17 (capitalization omitted).

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To prevail on a §10(b) claim, a plaintiff must show that the defendant made a statement that was "*misleading* as to a *material* fact."[4] *Basic*, 485 U. S., at 238. In *Basic*, we

[4]Under the Private Securities Litigation Reform Act of 1995 (PSLRA), when a plaintiff's claim is based on alleged misrepresentations or omissions of a material fact, "the complaint shall specify each

held that this materiality requirement is satisfied when there is "'a substantial likelihood that the disclosure of the omitted fact would have been viewed by the reasonable investor as having significantly altered the "total mix" of information made available.'" *Id.*, at 231–232 (quoting *TSC Industries, Inc.* v. *Northway, Inc.*, 426 U. S. 438, 449 (1976)). We were "careful not to set too low a standard of materiality," for fear that management would "'bury the shareholders in an avalanche of trivial information.'" 485 U. S., at 231 (quoting *TSC Industries*, 426 U. S., at 448–449).

Basic involved a claim that the defendant had made misleading statements denying that it was engaged in merger negotiations when it was, in fact, conducting preliminary negotiations. See 485 U. S., at 227–229. The defendant urged a bright-line rule that preliminary merger negotiations are material only once the parties to the negotiations reach an agreement in principle. *Id.*, at 232–233. We observed that "[a]ny approach that designates a single fact or occurrence as always determinative of an inherently fact-specific finding such as materiality, must necessarily be overinclusive or underinclusive." *Id.*, at 236. We thus rejected the defendant's proposed rule, explaining that it would "artificially exclud[e] from the definition of materiality information concerning merger discussions, which would otherwise be considered significant to the trading decision of a reasonable investor." *Ibid.*

Like the defendant in *Basic*, Matrixx urges us to adopt a bright-line rule that reports of adverse events[5] associated

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statement alleged to have been misleading, [and] the reason or reasons why the statement is misleading." 15 U. S. C. §78u–4(b)(1).

[5]The FDA defines an "[a]dverse drug experience" as "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 CFR §314.80(a) (2010). Federal law imposes certain obligations on pharmaceutical manufacturers to report

with a pharmaceutical company's products cannot be material absent a sufficient number of such reports to establish a statistically significant risk that the product is in fact causing the events.[6] Absent statistical significance, Matrixx argues, adverse event reports provide only "anecdotal" evidence that "the user of a drug experienced an adverse event at some point during or following the use of that drug." Brief for Petitioners 17. Accordingly, it contends, reasonable investors would not consider such reports relevant unless they are statistically significant because only then do they "reflect a scientifically reliable basis for inferring a potential causal link between product use and the adverse event." *Id.*, at 32.

As in *Basic*, Matrixx's categorical rule would "artificially exclud[e]" information that "would otherwise be considered significant to the trading decision of a reasonable investor." 485 U. S., at 236. Matrixx's argument rests on the premise that statistical significance is the only reliable indication of causation. This premise is flawed: As the SEC points out, "medical researchers . . . consider multiple

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adverse events to the FDA. During the class period, manufacturers of over-the-counter drugs such as Zicam Cold Remedy had no obligation to report adverse events to the FDA. In 2006, Congress enacted legislation to require manufacturers of over-the-counter drugs to report any "serious adverse event" to the FDA within 15 business days. See 21 U. S. C. §§379aa(b), (c).

[6] "A study that is statistically significant has results that are unlikely to be the result of random error . . . ." Federal Judicial Center, Reference Manual on Scientific Evidence 354 (2d ed. 2000). To test for significance, a researcher develops a "null hypothesis"—*e.g.*, the assertion that there is no relationship between Zicam use and anosmia. See *id.*, at 122. The researcher then calculates the probability of obtaining the observed data (or more extreme data) if the null hypothesis is true (called the *p*-value). *Ibid.* Small *p*-values are evidence that the null hypothesis is incorrect. See *ibid.* Finally, the researcher compares the *p*-value to a preselected value called the significance level. *Id.*, at 123. If the *p*-value is below the preselected value, the difference is deemed "significant." *Id.*, at 124.

factors in assessing causation." Brief for United States as *Amicus Curiae* 12. Statistically significant data are not always available. For example, when an adverse event is subtle or rare, "an inability to obtain a data set of appropriate quality or quantity may preclude a finding of statistical significance." *Id.*, at 15; see also Brief for Medical Researchers as *Amici Curiae* 11. Moreover, ethical considerations may prohibit researchers from conducting randomized clinical trials to confirm a suspected causal link for the purpose of obtaining statistically significant data. See *id.*, at 10–11.

A lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events. As Matrixx itself concedes, medical experts rely on other evidence to establish an inference of causation. See Brief for Petitioners 44–45, n. 22.[7] We note that courts frequently permit expert testimony on causation based on evidence other than statistical significance. See, *e.g.*, *Best* v. *Lowe's Home Centers, Inc.*, 563 F. 3d 171, 178 (CA6 2009); *Westberry* v. *Gislaved Gummi AB*, 178 F. 3d 257, 263–264 (CA4 1999) (citing cases); *Wells* v. *Ortho Pharmaceutical Corp.*, 788 F. 2d 741, 744–745 (CA11 1986). We need not consider whether the expert testimony was properly admitted in those cases, and we do not attempt to define here what constitutes reliable evidence of causation. It suffices to

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[7]Matrixx and its *amici* list as relevant factors the strength of the association between the drug and the adverse effects; a temporal relationship between exposure and the adverse event; consistency across studies; biological plausibility; consideration of alternative explanations; specificity (*i.e.*, whether the specific chemical is associated with the specific disease); the dose-response relationship; and the clinical and pathological characteristics of the event. Brief for Petitioners 44–45, n. 22; Brief for Consumer Healthcare Products Assn. et al. as *Amici Curiae* 12–13. These factors are similar to the factors the FDA considers in taking action against pharmaceutical products. See *infra*, at 13–14.

note that, as these courts have recognized, "medical professionals and researchers do not limit the data they consider to the results of randomized clinical trials or to statistically significant evidence." Brief for Medical Researchers as *Amici Curiae* 31.

The FDA similarly does not limit the evidence it considers for purposes of assessing causation and taking regulatory action to statistically significant data. In assessing the safety risk posed by a product, the FDA considers factors such as "strength of the association," "temporal relationship of product use and the event," "consistency of findings across available data sources," "evidence of a dose-response for the effect," "biologic plausibility," "seriousness of the event relative to the disease being treated," "potential to mitigate the risk in the population," "feasibility of further study using observational or controlled clinical study designs," and "degree of benefit the product provides, including availability of other therapies."[8] FDA, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment 18 (2005) (capitalization omitted), http://www.fda.gov/downloads/RegulatingInformation/Guidances/UCM126834.pdf (all Internet materials as visited Mar. 17, 2011, and available in Clerk of Court's case file); see also Brief for United States as *Amicus Curiae* 19–20 (same); FDA, The Clinical Impact of Adverse Event Reporting 6 (1996) (similar), http://www.fda.gov/downloads/safety/MedWatch/UCM168505.pdf. It "does not apply any single metric for determining when additional inquiry or action is necessary, and it certainly does not insist upon 'statistical significance.'" Brief for United States as *Amicus Curiae* 19.

Not only does the FDA rely on a wide range of evidence of causation, it sometimes acts on the basis of evidence that suggests, but does not prove, causation. For example,

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[8] See also n. 7, *supra*.

the FDA requires manufacturers of over-the-counter drugs to revise their labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 CFR §201.80(e). More generally, the FDA may make regulatory decisions against drugs based on postmarketing evidence that gives rise to only a suspicion of causation. See FDA, The Clinical Impact of Adverse Event Reporting, *supra*, at 7 ("[A]chieving certain proof of causality through postmarketing surveillance is unusual. Attaining a prominent degree of suspicion is much more likely, and may be considered a sufficient basis for regulatory decisions" (footnote omitted)).[9]

This case proves the point. In 2009, the FDA issued a warning letter to Matrixx stating that "[a] significant and growing body of evidence substantiates that the Zicam Cold Remedy intranasal products may pose a serious risk to consumers who use them." App. 270a. The letter cited as evidence 130 reports of anosmia the FDA had received, the fact that the FDA had received few reports of anosmia associated with other intranasal cold remedies, and "evidence in the published scientific literature that various salts of zinc can damage olfactory function in animals and

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[9] See also GAO, M. Crosse et al., Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process 7 (GAO–06–402, 2006) ("If FDA has information that a drug on the market may pose a significant health risk to consumers, it weighs the effect of the adverse events against the benefit of the drug to determine what actions, if any, are warranted. This decision-making process is complex and encompasses many factors, such as the medical importance and utility of the drug, the drug's extent of usage, the severity of the disease being treated, the drug's efficacy in treating this disease, and the availability of other drugs to treat the same disorder"), http://www.gao.gov/new.items/d06402.pdf; Federal Judicial Center, *supra* n. 6, at 33 ("[R]isk assessors may pay heed to any evidence that points to a need for caution, rather than assess the likelihood that a causal relationship in a specific case is more likely than not").

humans." *Ibid.* It did not cite statistically significant data.

Given that medical professionals and regulators act on the basis of evidence of causation that is not statistically significant, it stands to reason that in certain cases reasonable investors would as well. As Matrixx acknowledges, adverse event reports "appear in many forms, including direct complaints by users to manufacturers, reports by doctors about reported or observed patient reactions, more detailed case reports published by doctors in medical journals, or larger scale published clinical studies." Brief for Petitioners 17. As a result, assessing the materiality of adverse event reports is a "fact-specific" inquiry, *Basic*, 485 U. S., at 236, that requires consideration of the source, content, and context of the reports. This is not to say that statistical significance (or the lack thereof) is irrelevant—only that it is not dispositive of every case.

Application of *Basic*'s "total mix" standard does not mean that pharmaceutical manufacturers must disclose all reports of adverse events. Adverse event reports are daily events in the pharmaceutical industry; in 2009, the FDA entered nearly 500,000 such reports into its reporting system, see FDA, Reports Received and Reports Entered in AERS by Year (as of Mar. 31, 2010), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm. The fact that a user of a drug has suffered an adverse event, standing alone, does not mean that the drug caused that event. See FDA, Annual Adverse Drug Experience Report: 1996, p. 2 (1997), http://drugandevicelaw.net/Annual%20Adverse%20Drug%20Experience%20Report%201996.pdf. The question remains whether a *reasonable* investor would have viewed the nondisclosed information "'as having *significantly* altered the "total mix" of information made available.'" *Basic*, 485 U. S., at

232 (quoting *TSC Industries*, 426 U. S., at 449; emphasis added). For the reasons just stated, the mere existence of reports of adverse events—which says nothing in and of itself about whether the drug is causing the adverse events—will not satisfy this standard. Something more is needed, but that something more is not limited to statistical significance and can come from "the source, content, and context of the reports," *supra*, at 15. This contextual inquiry may reveal in some cases that reasonable investors would have viewed reports of adverse events as material even though the reports did not provide statistically significant evidence of a causal link.[10]

Moreover, it bears emphasis that §10(b) and Rule 10b–5(b) do not create an affirmative duty to disclose any and all material information. Disclosure is required under these provisions only when necessary "to make . . . statements made, in the light of the circumstances under which they were made, not misleading. 17 CFR §240.10b–5(b); see also *Basic*, 485 U. S., at 239, n. 17 ("Silence, absent a duty to disclose, is not misleading under Rule 10b–5"). Even with respect to information that a reasonable investor might consider material, companies can control what they have to disclose under these provisions by controlling what they say to the market.

2

Applying *Basic*'s "total mix" standard in this case, we conclude that respondents have adequately pleaded materiality. This is not a case about a handful of anecdotal

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[10] We note that our conclusion accords with views of the SEC, as expressed in an *amicus curiae* brief filed in this case. See Brief for United States as *Amicus Curiae* 11–12; see also *TSC Industries, Inc.* v. *Northway, Inc.*, 426 U. S. 438, 449, n. 10 (1976) ("[T]he SEC's view of the proper balance between the need to insure adequate disclosure and the need to avoid the adverse consequences of setting too low a threshold for civil liability is entitled to consideration").

reports, as Matrixx suggests. Assuming the complaint's allegations to be true, as we must, Matrixx received information that plausibly indicated a reliable causal link between Zicam and anosmia. That information included reports from three medical professionals and researchers about more than 10 patients who had lost their sense of smell after using Zicam. Clarot told Linschoten that Matrixx had received additional reports of anosmia. (In addition, during the class period, nine plaintiffs commenced four product liability lawsuits against Matrixx alleging a causal link between Zicam use and anosmia.)[11] Further, Matrixx knew that Linschoten and Dr. Jafek had presented their findings about a causal link between Zicam and anosmia to a national medical conference devoted to treatment of diseases of the nose.[12] Their presentation described a patient who experienced severe burning in his nose, followed immediately by a loss of smell, after using Zicam—suggesting a temporal relationship between Zicam use and anosmia.

Critically, both Dr. Hirsch and Linschoten had also drawn Matrixx's attention to previous studies that had demonstrated a biological causal link between intranasal application of zinc and anosmia.[13] Before his conversation

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[11] It is unclear whether these plaintiffs were the same individuals whose symptoms were reported by the medical professionals.

[12] Matrixx contends that Dr. Jafek and Linschoten's study was not reliable because they did not sufficiently rule out the common cold as a cause for their patients' anosmia. We note that the complaint alleges that, in one instance, a consumer who did not have a cold lost his sense of smell after using Zicam. More importantly, to survive a motion to dismiss, respondents need only allege "enough facts to state a claim to relief that is plausible on its face." *Bell Atlantic Corp.* v. *Twombly*, 550 U. S. 544, 570 (2007). For all the reasons we state in the opinion, respondents' allegations plausibly suggest that Dr. Jafek and Linschoten's conclusions were based on reliable evidence of a causal link between Zicam and anosmia.

[13] Matrixx contends that these studies are not reliable evidence of

with Linschoten, Clarot, Matrixx's vice president of research and development, was seemingly unaware of these studies, and the complaint suggests that, as of the class period, Matrixx had not conducted any research of its own relating to anosmia. See, *e.g.*, App. 84a (referencing a press report, issued after the end of the class period, noting that Matrixx said it would begin conducting "'animal and human studies to further characterize these post-marketing complaints'"). Accordingly, it can reasonably be inferred from the complaint that Matrixx had no basis for rejecting Dr. Jafek's findings out of hand.

We believe that these allegations suffice to "raise a reasonable expectation that discovery will reveal evidence" satisfying the materiality requirement, *Bell Atlantic Corp.* v. *Twombly*, 550 U. S. 544, 556 (2007), and to "allo[w] the court to draw the reasonable inference that the defendant is liable for the misconduct alleged," *Iqbal*, 556 U. S., at ___ (slip op., at 14). The information provided to Matrixx by medical experts revealed a plausible causal relationship between Zicam Cold Remedy and anosmia. Consumers likely would have viewed the risk associated with Zicam (possible loss of smell) as substantially outweighing the benefit of using the product (alleviating cold symptoms), particularly in light of the existence of many alternative products on the market. Importantly, Zicam Cold Remedy allegedly accounted for 70 percent of Matrixx's sales. Viewing the allegations of the complaint as a whole,

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causation because the studies used zinc sulfate, whereas the active ingredient in Matrixx is zinc gluconate. Respondents' complaint, however, alleges that the studies confirmed the toxicity of "zinc." App. 68a. Matrixx further contends that studies relating to fish cannot reliably prove causation with respect to humans. The complaint references several studies, however, only one of which involved fish. In any event, the existence of the studies suggests a plausible biological link between zinc and anosmia, which, in combination with the other allegations, is sufficient to survive a motion to dismiss.

the complaint alleges facts suggesting a significant risk to the commercial viability of Matrixx's leading product.

It is substantially likely that a reasonable investor would have viewed this information "'as having significantly altered the "total mix" of information made available.'" *Basic*, 485 U. S., at 232 (quoting *TSC Industries*, 426 U. S., at 449). Matrixx told the market that revenues were going to rise 50 and then 80 percent. Assuming the complaint's allegations to be true, however, Matrixx had information indicating a significant risk to its leading revenue-generating product. Matrixx also stated that reports indicating that Zicam caused anosmia were "'completely unfounded and misleading'" and that "'the safety and efficacy of zinc gluconate for the treatment of symptoms related to the common cold have been well established.'" App. 77a–78a. Importantly, however, Matrixx had evidence of a biological link between Zicam's key ingredient and anosmia, and it had not conducted any studies of its own to disprove that link. In fact, as Matrixx later revealed, the scientific evidence at that time was "'insufficient . . . to determine if zinc gluconate, when used as recommended, affects a person's ability to smell.'" *Id.*, at 82a.

Assuming the facts to be true, these were material facts "necessary in order to make the statements made, in the light of the circumstances under which they were made, not misleading." 17 CFR §240.10b–5(b). We therefore affirm the Court of Appeals' holding that respondents adequately pleaded the element of a material misrepresentation or omission.

B

Matrixx also argues that respondents failed to allege facts plausibly suggesting that it acted with the required level of scienter. "To establish liability under §10(b) and Rule 10b–5, a private plaintiff must prove that the defen-

dant acted with scienter, 'a mental state embracing intent to deceive, manipulate, or defraud.'" *Tellabs*, 551 U. S., at 319 (quoting *Ernst & Ernst* v. *Hochfelder*, 425 U. S. 185, 193–194, and n. 12 (1976)). We have not decided whether recklessness suffices to fulfill the scienter requirement. See *Tellabs*, 551 U. S., at 319, n. 3. Because Matrixx does not challenge the Court of Appeals' holding that the scienter requirement may be satisfied by a showing of "deliberate recklessness," see 585 F. 3d, at 1180 (internal quotation marks omitted), we assume, without deciding, that the standard applied by the Court of Appeals is sufficient to establish scienter.[14]

Under the PSLRA, a plaintiff must "state with particularity facts giving rise to a strong inference that the defendant acted with the required state of mind." 15 U. S. C. A. §78u–4(b)(2)(A) (Feb. 2011 Supp.). This standard requires courts to take into account "plausible opposing inferences." *Tellabs*, 551 U. S., at 323. A complaint adequately pleads scienter under the PSLRA "only if a reasonable person would deem the inference of scienter cogent and at least as compelling as any opposing inference one could draw from the facts alleged." *Id.*, at 324. In making this determination, the court must review "all the allegations holistically." *Id.*, at 326. The absence of a motive allegation, though relevant, is not dispositive. *Id.*, at 325.

Matrixx argues, in summary fashion, that because respondents do not allege that it knew of statistically significant evidence of causation, there is no basis to consider the inference that it acted recklessly or knowingly to be at least as compelling as the alternative infer-

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[14] Under the PSLRA, if the alleged misstatement or omission is a "forward-looking statement," the required level of scienter is "actual knowledge." 15 U. S. C. §78u–5(c)(1)(B). Matrixx has not argued that the statements or omissions here are "forward-looking statement[s]."

ences. "Rather," it argues, "the most obvious inference is that petitioners did not disclose the [reports] simply because petitioners believed they were far too few . . . to indicate anything meaningful about adverse reactions to use of Zicam." Brief for Petitioners 49. Matrixx's proposed bright-line rule requiring an allegation of statistical significance to establish a strong inference of scienter is just as flawed as its approach to materiality.

The inference that Matrixx acted recklessly (or intentionally, for that matter) is at least as compelling, if not more compelling, than the inference that it simply thought the reports did not indicate anything meaningful about adverse reactions. According to the complaint, Matrixx was sufficiently concerned about the information it received that it informed Linschoten that it had hired a consultant to review the product, asked Linschoten to participate in animal studies, and convened a panel of physicians and scientists in response to Dr. Jafek's presentation. It successfully prevented Dr. Jafek from using Zicam's name in his presentation on the ground that he needed Matrixx's permission to do so. Most significantly, Matrixx issued a press release that suggested that studies had confirmed that Zicam does not cause anosmia when, in fact, it had not conducted any studies relating to anosmia and the scientific evidence at that time, according to the panel of scientists, was insufficient to determine whether Zicam did or did not cause anosmia.[15]

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[15] One of Matrixx's *amici* argues that "the most cogent inference regarding Matrixx's state of mind is that it delayed releasing information regarding anosmia complaints in order to provide itself an opportunity to carefully review all evidence regarding any link between Zicam and anosmia." Brief for Washington Legal Foundation as *Amicus Curiae* 26. We do not doubt that this may be the most cogent inference in some cases. Here, however, the misleading nature of Matrixx's press release is sufficient to render the inference of scienter at least as compelling as the inference suggested by *amicus*.

These allegations, "taken collectively," give rise to a "cogent and compelling" inference that Matrixx elected not to disclose the reports of adverse events not because it believed they were meaningless but because it understood their likely effect on the market. *Tellabs*, 551 U. S., at 323, 324. "[A] reasonable person" would deem the inference that Matrixx acted with deliberate recklessness (or even intent) "at least as compelling as any opposing inference one could draw from the facts alleged." *Id.*, at 324. We conclude, in agreement with the Court of Appeals, that respondents have adequately pleaded scienter. Whether respondents can ultimately prove their allegations and establish scienter is an altogether different question.

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For the reasons stated, the judgment of the Court of Appeals for the Ninth Circuit is

Affirmed.

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First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects

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ABSTRACT

BACKGROUND

The risk of birth defects after antenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) remains controversial.

METHODS

We assessed associations between first-trimester maternal use of SSRIs and the risk of birth defects among 9849 infants with and 5860 infants without birth defects participating in the Slone Epidemiology Center Birth Defects Study.

RESULTS

In analyses of defects previously associated with SSRI use (involving 42 comparisons), overall use of SSRIs was not associated with significantly increased risks of craniosynostosis (115 subjects, 2 exposed to SSRIs; odds ratio, 0.8; 95% confidence interval [CI], 0.2 to 3.5), omphalocele (127 subjects, 3 exposed; odds ratio, 1.4; 95% CI, 0.4 to 4.5), or heart defects overall (3724 subjects, 100 exposed; odds ratio, 1.2; 95% CI, 0.9 to 1.6). Analyses of the associations between individual SSRIs and specific defects showed significant associations between the use of sertraline and omphalocele (odds ratio, 5.7; 95% CI, 1.6 to 20.7; 3 exposed subjects) and septal defects (odds ratio, 2.0; 95% CI, 1.2 to 4.0; 13 exposed subjects) and between the use of paroxetine and right ventricular outflow tract obstruction defects (odds ratio, 3.3; 95% CI, 1.3 to 8.8; 6 exposed subjects). The risks were not appreciably or significantly increased for other defects or other SSRIs or non-SSRI antidepressants. Exploratory analyses involving 66 comparisons showed possible associations of paroxetine and sertraline with other specific defects.

CONCLUSIONS

Our findings do not show that there are significantly increased risks of craniosynostosis, omphalocele, or heart defects associated with SSRI use overall. They suggest that individual SSRIs may confer increased risks for some specific defects, but it should be recognized that the specific defects implicated are rare and the absolute risks are small.

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Symptoms of clinical depression affect 8 to 20% of women[1,2]; during pregnancy, about 10% of women are affected,[3] and many of these women are treated with antidepressants. In the late 1980s, a new class of antidepressants, selective serotonin-reuptake inhibitors (SSRIs), appeared and rapidly gained widespread acceptance because they have fewer side effects than the older tricyclic antidepressants and pose less risk when taken in overdose.[4] However, concern has been raised about their potential effects on the fetus. Neonatal effects, known as "SSRI neonatal withdrawal syndrome" or "SSRI abstinence syndrome,"[5-9] are now well established, but the relation of antenatal SSRI exposure to birth defects remains controversial.

Early studies[9-15] demonstrated that SSRIs were not "major teratogens" similar to thalidomide or isotretinoin.[16] More recently, however, elevated risks of birth defects overall,[17,18] as well as elevated risks of omphalocele,[19] craniosynostosis,[19] and congenital heart defects,[18,20-22] have been reported in association with the use of SSRIs. One study specifically identified paroxetine as increasing the risk of omphalocele,[19] and three have associated this SSRI with congenital heart defects.[20-22] However, none of these studies considered risks of cardiac defects in relation to other specific SSRIs. Using data from the Slone Epidemiology Center Birth Defects Study, an ongoing program of case–control surveillance of medications in relation to birth defects, we evaluated these hypotheses and also considered other specific birth defects in relation to first-trimester use of specific SSRIs.

METHODS

STUDY DESIGN

The Birth Defects Study began in 1976, focusing both on testing existing hypotheses and on identifying previously unsuspected associations; the methods have been described.[23,24] Infants with any of a wide range of malformations are identified in five study centers that include the areas surrounding Boston, Philadelphia, Toronto, and San Diego, as well as a portion of New York State. Research staff identify subjects by reviewing clinical and surgical logs, reviewing admission and discharge lists, and contacting newborn nurseries and labor and delivery rooms. Subjects in New York State and, since 1998, in Massachusetts are identified from statewide birth-defect registries. Infants with isolated minor defects (e.g., accessory nipples, dislocatable hips, and low-set ears) are excluded. Nonmalformed infants were identified at study hospitals until 1998; subsequently, enrollment was expanded to include a population-based random sample of newborns in Massachusetts. This study has been approved by the institutional review boards at Boston University and other participating institutions.

Mothers of identified infants are invited to participate by completing a 45-to-60-minute interview (in person until 1998 and by telephone thereafter) within 6 months after delivery, conducted by trained study nurses who are unaware of the study hypotheses. Oral informed consent is obtained from the mothers. The interview elicits information on demographic, reproductive, and medical factors, cigarette smoking, and the consumption of alcohol and caffeine. Detailed data are collected on all medications (prescription, over-the-counter, vitamins and minerals, and herbal products) used at any time from 2 months before conception through the end of the pregnancy.

Using a multilevel approach,[25] we first ask women whether they had any of a list of specific illnesses during pregnancy and what drugs they used to treat those conditions. We then ask about use of medications for specific indications, including "anxiety," "depression," and "other psychological conditions." Finally, independent of their responses to the previous questions, each woman is asked about her use of named medications, identified by brand name, including Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Effexor (venlafaxine), Elavil (amitriptyline), Celexa (citalopram), Luvox (fluvoxamine), Lexapro (escitalopram), and Wellbutrin (bupropion).

The current analysis was restricted to women whose last menstrual period occurred between January 1, 1993, and December 31, 2004. We excluded subjects whose infants had chromosomal defects, known mendelian inherited disorders, syndromes, defects with a known cause (e.g., fetal alcohol syndrome), and metabolic disorders (e.g., phenylketonuria and glucose-6-phosphate dehydrogenase deficiency). Among subjects, 22.7% of mothers and 25.4% of controls declined to participate. Another 15.6% of mothers and 14.7% of controls either did not respond to repeated contacts or were unavailable for interview.

ASSESSMENT OF PREVIOUSLY REPORTED ASSOCIATIONS

Previous reports have associated craniosynostosis, omphalocele, and congenital heart defects with the use of SSRIs. Because heart defects represent developmentally diverse outcomes, we created seven developmentally based subgroups.[26] In order of embryologic development, these are looping, laterality, and single-ventricle defects (e.g., situs inversus totalis and double-inlet left ventricle); conotruncal defects (e.g., tetralogy of Fallot and double-outlet right ventricle); atrioventricular canal defects (e.g., endocardial cushion defect and common atrioventricular canal defect); right ventricular outflow tract obstruction (e.g., pulmonary valve atresia or stenosis and Ebstein's anomaly); left ventricular outflow tract obstruction (e.g., aortic valve atresia or stenosis and hypoplastic left heart); septal defects (e.g., ventricular septal defect and atrial septal defect); and total or partial anomalous pulmonary venous return. A complete list is provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

A clinical geneticist trained in pediatric cardiology reviewed the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), codes of each case and, where possible, assigned the case to one or more of the seven groups. Cases were assigned to as many of these categories as their ICD codes would indicate, but in some situations, considerations of developmental processes took precedence. For example, a case with anomalous pulmonary venous return and a septal defect, along with the additional diagnosis of asplenia, was assigned to the developmentally appropriate category of "laterality defect."

EXPLORATORY ANALYSES

In addition to the defects previously associated with SSRIs, we examined other specific defects that were present in at least 100 subjects overall and at least 5 exposed subjects.

EXPOSURE

We considered first-trimester exposure to include use of any SSRI from 28 days before the last menstrual period through the fourth lunar month (112 days after the last menstrual period). The analysis of specific SSRIs excluded 79 women who took more than one SSRI during this period. To consider possible "confounding by indication," in which an apparent association between an outcome and medication is actually due to the condition for which the medication is used, we also investigated exposure to non-SSRI antidepressants (e.g., tricyclic antidepressants, bupropion, and venlafaxine; the latter has both serotonin and norepinephrine activity and represented 20% of this group). The reference group for all analyses was women not exposed to any antidepressant at any time from 56 days before the last menstrual period through the end of pregnancy. To avoid misclassification, we excluded women whose only exposure to antidepressants was between 28 and 56 days before the last menstrual period or after lunar month 4.

STATISTICAL ANALYSIS

Odds ratios and 95% confidence intervals were calculated separately for each exposure and outcome by multiple logistic regression. To assess confounding, we explored factors that were associated with exposure to any SSRI and to the risk of birth defects overall, including maternal age, maternal race or ethnic group (self-reported), maternal education, year of last menstrual period, parity, study center, first-trimester smoking, first-trimester alcohol consumption, history of a birth defect in a first-degree relative, prepregnant body-mass index, seizures, diabetes mellitus, hypertension, infertility, and first-trimester use of folic acid. Because some birth defects have been associated with obesity,[27-30] we also explored effect modification by body-mass index for each outcome with an increased risk. No statistical adjustment was made for multiple testing.

RESULTS

A total of 9849 infants with malformations and 5860 control infants were included in the analysis. Among outcomes previously reported to be associated with SSRI use, there were 127 cases of omphalocele, 115 cases of craniosynostosis, and 3724 cases of congenital heart defects; the latter included 186 looping or laterality defects, 620 conotruncal defects, 164 atrioventricular defects, 363 right ventricular outflow tract obstruction defects, 482 left ventricular outflow tract obstruction defects, 1161 septal defects, and 17 cases of anomalous pulmonary venous return.

For exploratory analyses, we identified 17 diagnosis groups that had 100 or more subjects. Six

groups were excluded from further analysis because they had fewer than 5 subjects who had been exposed to an SSRI: esophageal atresia (189 subjects, 4 exposed), absent kidney (178 subjects, 4 exposed), horseshoe or accessory kidney (127 subjects, 4 exposed), abnormal intestinal rotation (149 subjects, 3 exposed), cystic kidney (179 subjects, 2 exposed), and small intestinal atresia (129 subjects, 2 exposed).

Table 1 shows the rates of exposure to any SSRI, specific SSRIs, and non-SSRI antidepressants for each outcome and for the control subjects, who had no malformations. Because few subjects had been exposed to fluvoxamine (five subjects) and escitalopram (eight subjects), these medications were not considered further. Similarly, we did not analyze looping and laterality defects (two SSRI-exposed subjects), atrioventricular canal defects (no SSRI-exposed subjects), and anomalous pulmonary venous return (no SSRI-exposed subjects).

ASSESSMENT OF PREVIOUS HYPOTHESES

Table 2 shows the results for the 42 comparisons related to craniosynostosis, omphalocele, congenital heart defects, and the four specific cardiac-defect groups, adjusted for potential confounders.

There was no significant increase in the risk of craniosynostosis associated with the use of SSRIs overall or with individual SSRIs; only 2 of 115 subjects with craniosynostosis had been exposed to an SSRI (1 to sertraline and 1 to paroxetine). For omphalocele, 3 of 127 subjects had been exposed to an SSRI, all to sertraline (odds ratio, 5.7; 95% confidence interval [CI], 1.6 to 20.7).

We found no appreciable or significantly increased risk of congenital heart defects overall in relation to the use of SSRIs overall (odds ratio, 1.2; 95% CI, 0.9 to 1.6). However, when we assessed associations between specific heart-defect subgroups and individual SSRIs, the odds ratios ranged from 0.5 to 3.3, and two risk estimates had lower bounds that exceeded 1.0: sertraline

Table 1. Rates of Exposure to Antidepressants within Outcome Groups.

Outcome	Total No. of Subjects	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Antidepressant
				no. of subjects (%)			
Craniosynostosis	115	2 (1.7)	0	1 (0.9)	1 (0.9)	0	0
Omphalocele	127	3 (2.4)	0	3 (2.4)	0	0	1 (0.8)
Any cardiac defect	3724	100 (2.7)	31 (0.8)	32 (0.9)	25 (0.7)	5 (0.1)	23 (0.6)
Conotruncal defects	620	13 (2.1)	6 (1.0)	2 (0.3)	4 (0.6)	0	4 (0.6)
Right ventricular outflow tract obstruction defects	363	15 (4.1)	4 (1.1)	3 (0.8)	6 (1.7)	0	2 (0.6)
Left ventricular outflow tract obstruction defects	482	15 (3.1)	6 (1.2)	5 (1.0)	1 (0.2)	2 (0.4)	2 (0.4)
Septal defects	1161	32 (2.8)	10 (0.9)	13 (1.1)	6 (0.5)	2 (0.2)	10 (0.9)
Cleft lip with or without cleft palate	704	22 (3.1)	11 (1.6)	3 (0.4)	4 (0.6)	4 (0.6)	6 (0.9)
Pyloric stenosis	688	18 (2.6)	6 (0.9)	7 (1.0)	3 (0.4)	2 (0.3)	6 (0.9)
Renal-collecting-system defects	644	17 (2.6)	5 (0.8)	6 (0.9)	4 (0.6)	2 (0.3)	4 (0.6)
Hypospadias	497	14 (2.8)	3 (0.6)	3 (0.6)	3 (0.6)	4 (0.8)	5 (1.0)
Clubfoot	413	20 (4.8)	3 (0.7)	5 (1.2)	10 (2.4)	2 (0.5)	4 (1.0)
Cleft palate alone	377	7 (1.9)	3 (0.8)	0	3 (0.8)	1 (0.3)	3 (0.8)
Undescended testis	349	11 (3.2)	1 (0.3)	0	6 (1.7)	2 (0.6)	2 (0.6)
Neural-tube defects	320	5 (1.6)	0	1 (0.3)	4 (1.2)	0	1 (0.3)
Anal atresia	215	7 (3.3)	2 (0.9)	3 (1.4)	1 (0.5)	1 (0.5)	3 (1.4)
Diaphragmatic hernia	192	6 (3.1)	3 (1.6)	1 (0.5)	1 (0.5)	0	2 (1.0)
Limb-reduction defects	193	9 (4.7)	3 (1.6)	3 (1.6)	1 (0.5)	1 (0.5)	1 (0.5)
No malformations	5860	160 (2.7)	61 (1.0)	46 (0.8)	30 (0.5)	15 (0.3)	49 (0.8)

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Specific SSRIs in Relation to Outcomes Previously Reported to Be Associated with SSRI Use.*

Outcome	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Antidepressant
			odds ratio (95% confidence interval)			
Craniosynostosis	0.8 (0.2–3.5)	—	1.8 (0.2–14.9)	1.7 (0.2–14.4)	—	—
Omphalocele	1.4 (0.4– 4.5)	—	5.7 (1.6–20.7)	—	—	1.2 (0.2–9.3)
Any cardiac defect	1.2 (0.9–1.6)	0.9 (0.6–1.5)	1.5 (0.9–2.6)	1.4 (0.8–2.5)	0.7 (0.2–2.1)	0.8 (0.5–1.5)
Conotruncal defects	1.2 (0.6–2.1)	1.3 (0.5–3.2)	0.7 (0.2–3.3)	1.7 (0.6–5.1)	—	0.9 (0.3–2.6)
Right ventricular outflow tract obstruction defects	2.0 (1.1–3.6)	1.0 (0.2–3.4)	2.0 (0.6–6.8)	3.3 (1.3–8.8)	—	0.9 (0.2–3.8)
Left ventricular outflow tract obstruction defects	1.6 (0.9–2.9)	1.6 (0.6–4.0)	1.9 (0.6–5.8)	0.5 (0.1–3.9)	3.3 (0.7–16.0)	0.6 (0.1–2.4)
Septal defects	1.2 (0.8–1.8)	1.0 (0.5–2.2)	2.0 (1.2–4.0)	0.8 (0.3–2.2)	0.8 (0.2–4.0)	1.1 (0.6–2.4)

* Odds ratios are adjusted for maternal age; maternal race or ethnic group (self-reported); maternal education; year of last menstrual period; study center; first-trimester smoking status; first-trimester alcohol consumption; history of a birth defect in a first-degree relative; prepregnancy body-mass index; parity; presence or absence of seizures, diabetes mellitus, hypertension, or infertility; and first-trimester use of folic acid. The reference group was all women not exposed to any antidepressant. Dashes indicate no exposed subjects.

in relation to septal defects (odds ratio, 2.0; 95% CI, 1.2 to 4.0, based on 13 exposed subjects) and paroxetine in relation to right ventricular outflow tract obstruction defects (odds ratio, 3.3; 95% CI, 1.3 to 8.8, based on 6 exposed subjects). No appreciable or significantly increased risks were associated with fluoxetine (range of odds ratios, 1.0 to 1.6), nor were there appreciable or significant associations between non-SSRI antidepressants and any of the specific birth defects examined.

EXPLORATORY ANALYSES

Table 3 presents risk estimates for other birth defects, adjusted for potential confounders. Among 66 comparisons, 4 had lower confidence bounds that exceeded 1.0: sertraline in relation to anal atresia and limb-reduction defects (3 exposed subjects for each defect) and paroxetine in relation to neural-tube defects and clubfoot (4 and 10 exposed subjects, respectively). One association, that between paroxetine use and undescended testis, had a lower confidence bound of 1.0. For non-SSRI antidepressants, risk estimates ranged from 0.6 to 1.2, with one exception: an odds ratio of 2.2 for anal atresia, based on three exposed subjects (lower 95% confidence bound, 0.6). For positive associations, no mothers of exposed subjects reported exposure to any suspected teratogenic drugs.[17]

We also investigated effect modification by body-mass index for associations with elevated risks. Although there was a tendency for risks to be higher in overweight and obese women than in women of normal weight, there were too few exposed women in each category to generate stable results (data not shown).

DISCUSSION

Our analysis did not confirm previously reported associations between overall use of SSRIs and craniosynostosis, omphalocele, or heart defects as a group. Alwan et al.[19] previously reported increased risks of craniosynostosis and omphalocele associated with maternal SSRI use and found paroxetine to be most strongly associated with omphalocele. We did not replicate these findings: no infant with omphalocele and only one with craniosynostosis was exposed to paroxetine among our study population. The only significant association we found between either of these two defects and the use of SSRIs was an association between sertraline use and omphalocele (odds ratio, 5.7; 95% CI, 1.6 to 20.7), which was based on only three exposed subjects.

We did not find significantly increased risks of congenital heart defects overall associated with overall use of SSRIs or of non-SSRI antidepressants. However, using an embryologically based

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for Specific SSRIs in Relation to Outcomes Not Previously Reported to Be Associated wtih SSRI Use.*

Outcome	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Antidepressant
			odds ratio (95% confidence interval)			
Cleft lip with or without cleft palate	1.5 (0.9–2.5)	1.8 (0.8–3.8)	1.1 (0.3–3.8)	1.2 (0.4–3.6)	3.2 (0.9–11.9)	1.2 (0.2–9.3)
Pyloric stenosis	1.1 (0.6–1.8)	0.9 (0.4–2.1)	1.7 (0.7–4.1)	0.7 (0.2–2.6)	2.1 (0.4–10.4)	1.1 (0.5–3.1)
Renal-collecting-system defects	1.1 (0.7–1.9)	1.0 (0.5–2.3)	1.7 (0.7–4.2)	1.0 (0.3–3.3)	1.9 (0.4–8.8)	0.7 (0.2–3.2)
Hypospadias	1.2 (0.6–2.2)	0.7 (0.2–2.4)	1.2 (0.4–4.2)	1.0 (0.3–3.3)	1.9 (0.4–8.8)	0.7 (0.3–2.4)
Clubfoot	2.2 (1.4–3.6)	0.8 (0.2–2.5)	2.4 (0.9–6.2)	5.8 (2.6–12.8)	2.7 (0.5–13.1)	1.0 (0.3–3.2)
Cleft palate alone	0.9 (0.4–2.0)	1.0 (0.3–3.5)	—	1.5 (0.4–5.3)	2.3 (0.4–12.6)	0.9 (0.3–3.2)
Undescended testis	1.3 (0.7–2.5)	0.4 (0.1–2.6)	—	2.8 (1.0–7.8)	3.1 (0.6–15.5)	0.7 (0.2–3.0)
Neural-tube defects	0.6 (0.2–1.4)	—	0.8 (0.1–6.3)	3.3 (1.1–10.4)	—	0.6 (0.1–2.4)
Anal atresia	1.9 (0.8–4.3)	1.4 (0.3–6.1)	4.4 (1.2–16.4)	1.0 (0.1–7.8)	3.0 (0.3–28.2)	2.2 (0.6–7.8)
Diaphragmatic hernia	1.8 (0.7–4.2)	2.0 (0.6–6.9)	1.5 (0.2–11.5)	1.2 (0.2–8.9)	—	1.1 (0.3–5.1)
Limb-reduction defects	1.7 (0.9–3.4)	1.7 (0.5–5.7)	3.9 (1.1–13.5)	1.0 (0.1–8.3)	4.0 (0.5–33.9)	0.7 (0.7–5.2)

* Odds ratios are adjusted for maternal age; maternal race or ethnic group (self-reported); maternal education; year of last menstrual period; study center; first-trimester smoking status; first-trimester alcohol consumption; history of a birth defect in a first-degree relative; prepregnancy body-mass index; parity; presence or absence of seizures, diabetes mellitus, hypertension, or infertility; and first-trimester use of folic acid. The reference group was all women not exposed to any antidepressant. Dashes indicate no exposed subjects.

classification of heart defects, we found a doubling of the risk of septal defects associated with sertraline use (odds ratio, 2.0), based on 13 exposed subjects, and a tripling of the risk of right ventricular outflow tract obstruction defects associated with paroxetine use (odds ratio, 3.3), based on 6 exposed subjects. The latter finding is supported by an odds ratio of 2.5, based on seven exposed subjects (95% CI, 1.0 to 9.6), identified by Alwan et al. in an article in this issue of the *Journal*.[31] These more detailed findings were derived from two case–control surveillance studies with data sets large enough to consider both specific malformations and specific SSRIs.

Our observations of significant increases in the risk of selected cardiac defects with the use of certain SSRIs may reflect different teratologic effects among specific drugs within a given pharmacologic class.[32] For SSRIs, this possibility is supported by the fact that various class members have parent compounds and metabolites with different pharmacologic characteristics.[33-35] However, we cannot rule out the possibility of chance associations, given the multiple comparisons performed.

The previously unreported associations we identified warrant particularly cautious interpretation. In the absence of preexisting hypotheses and the presence of multiple comparisons, distinguishing random variation from true elevations in risk is difficult. Despite the large size of our study overall, we had limited numbers to evaluate associations between rare outcomes and rare exposures. We included results based on small numbers of exposed subjects in order to allow other researchers to compare their observations with ours, but we caution that these estimates should not be interpreted as strong evidence of increased risks. On the basis of the magnitude of the risk estimate and the number of exposed subjects, certain associations warrant further exploration: sertraline in relation to anal atresia and limb-reduction defects, and paroxetine in relation to neural-tube defects and clubfoot.

Among all defects evaluated, we found that, for fluoxetine, no risk estimate exceeded 2.0 and none had a lower confidence bound exceeding 1.0. For non-SSRI antidepressants, no risk estimate exceeded 1.2, except for anal atresia, and the confidence interval for that estimate, based on three exposed subjects, did not exclude 1.0. On the other hand, sertraline and paroxetine were

associated with significant increases in specific birth defects, none of which were common to both drugs.

Recall bias may be a concern, since mothers of infants with malformations may recall and report exposures more completely than mothers of the control subjects who had no malformations. However, we consider this unlikely, since antidepressants are typically used on a regular basis for nontrivial indications, and recall of their use may be less subject to such bias than medications used infrequently and more casually. Further, the use of a multilevel structured questionnaire to identify medication use should minimize recall bias[25] and has been shown to elicit rates of use similar to estimates from marketing data.[36] Moreover, the null effects we observed among the non-SSRI antidepressants argue against recall bias, and recall bias would not explain risks associated with some individual SSRIs but not with others. Selection bias is unlikely, since mothers are invited to participate without knowledge of exposure. Detection bias is also unlikely, given the differential effects of non-SSRIs as compared with specific SSRIs and variability in the effects among specific SSRIs.

Confounding by uncontrolled factors is always possible in observational studies. We considered a large number of relevant demographic, medical, and reproductive factors. A major potential confounder is the effect of depression itself, unrelated to drug treatment. However, the absence of significantly increased risks of various birth defects associated with the use of non-SSRI antidepressants suggests that depression itself is unlikely to be the cause of the defects studied. The possibility that chance accounts for some or all of these results cannot be ruled out, especially in view of the many comparisons that were made in these analyses (42 in assessing previously reported associations and 66 in exploratory analyses). For that reason, we place greater reliance on findings that are consistent with previous studies, and we await further research on newly reported associations.

Our understanding of the risks to the fetus of SSRI use has evolved from initial small cohort studies that ruled out major teratogenic risks to more recent efforts that have raised questions about moderate overall increases in risk as well as increases in broad categories of defects, such as cardiac anomalies. The current study suggests that specific SSRIs may increase the risk of specific birth defects, and further studies will need sufficient power to pursue these important clinical questions. In the meantime, it is important to keep in perspective that the absolute risks of these rare defects are small. For example, the baseline prevalences of anal atresia[37] and right ventricular outflow tract obstruction defects[26] are each estimated to be about 5.5 cases per 10,000 live births; thus, even if a specific SSRI increased rates by a factor of four, the risk of having an affected child would still be only 0.2%.

The Slone Epidemiology Center Birth Defects Study was supported in part by grants from the National Institute of Child Health and Human Development (HD27697) and the National Heart, Lung, and Blood Institute (HL50763). Additional support was provided by Aventis and Sanofi Pasteur. This data analysis was supported in part by a contract from GlaxoSmithKline, the manufacturer of Paxil (paroxetine). Responsibility for this analysis and the manuscript rests solely with the authors.

Drs. Louik, Mitchell, and Werler report receiving support from Sanofi Pasteur to identify rates of use of various vaccines in pregnancy. Dr. Mitchell reports participating (unpaid) in an advisory committee for GlaxoSmithKline's Lamotrigine Pregnancy Registry and serving as principal investigator of the Isotretinoin Survey (2002–2006), sponsored by Barr Pharmaceuticals, Ranbaxy Laboratories, and Genpharm; all these companies manufacture generic forms of antidepressants included in this study. Dr. Werler reports participating in scientific advisory boards for pregnancy registries of rheumatoid arthritis medications marketed by Sanofi-Aventis, Abbott Laboratories, and Amgen. No other potential conflict of interest relevant to this article was reported.

We thank Dawn Jacobs, Fiona Rice, Rita Krolak, Kathleen Sheehan, Karen Bennett Mark, Clare Coughlin, Nastia Dynkin, Nancy Rodriquez-Sheridan, and Meghan Malone-Moses for their assistance in data collection and computer programming; the staff of the Massachusetts Department of Public Health Center for Birth Defects Research and Prevention, Charlotte Druschel and the New York State Health Department, and Christina Chambers and Kenneth Jones of the University of California, San Diego (UCSD), as well as the medical and nursing staff at the following participating hospitals for assistance with case ascertainment: Baystate Medical Center, Beth Israel Deaconess Medical Center, Boston Medical Center, Brigham and Women's Hospital, Brockton Hospital, Cambridge Hospital, Caritas Good Samaritan Medical Center, Charlton Memorial Hospital, Boston Children's Hospital, Emerson Hospital, Falmouth Hospital, Haverhill–Hale Hospital, Jordan Hospital, Kent Hospital, Lawrence General Hospital, Lowell General Hospital, Melrose–Wakefield Hospital, Metro West Medical Center–Framingham, Mt. Auburn Hospital, New England Medical Center, Newton–Wellesley Hospital, North Shore Medical Center, Rhode Island Hospital, Saints Memorial Medical Center, South Shore Hospital, Southern New Hampshire Medical Center, St. Elizabeth's Medical Center, St. Luke's Hospital, St. Vincent Hospital, University of Massachusetts Memorial Health Care, Women & Infants' Hospital, Abington Memorial Hospital, Albert Einstein Medical Center, Alfred I. duPont Hospital for Children, Bryn Mawr Hospital, Chester County Hospital, Children's Hospital of Philadelphia, Christiana Care Health Services, Community Hospital, Crozer–Chester Medical Center, Doylestown Hospital, Frankford Hospital, Hahnemann University

Hospital, the Hospital of the University of Pennsylvania, Lankenau Hospital, Lancaster General Hospital, Lehigh Valley Hospital, Nanticoke Memorial Hospital, Pennsylvania Hospital, Sacred Heart Hospital, St. Christopher's Hospital for Children, St. Mary Medical Center, Temple University Health Sciences Center, Reading Hospital & Medical Center, Thomas Jefferson University Hospital, Grand River Hospital, Guelph General Hospital, Hamilton Health Sciences Corporation, the Hospital for Sick Children, Humber River Regional Hospital–Church Site, Humber River Regional Hospital–Finch Site, Joseph Brant Memorial Hospital, Lakeridge Health Corporation, London Health Sciences Center, Mt. Sinai Hospital, North York General Hospital, Oakville Trafalgar Memorial Hospital, Scarborough Hospital–General Division, Scarborough Hospital–Grace Division, St. Joseph's Health Centre–London, St. Joseph's Health Centre–Toronto, St. Joseph's Healthcare–Hamilton, St. Michael's Hospital, Sunnybrook & Women's College Health Sciences Center, Toronto East General Hospital, Toronto General Hospital, Trillium Health Center, William Osler Heath Centre, York Central Hospital, York County Hospital, Alvarado Hospital, Balboa Naval Medical Center, Camp Pendleton Naval Hospital, Children's Hospital and Health Center, Kaiser Zion Medical Center, Palomar Medical Center, Pomerado Hospital, Scripps Mercy Hospital, Scripps Memorial Hospital–Chula Vista, Scripps Memorial Hospital–Encinitas, Scripps Memorial Hospital–La Jolla, Sharp Chula Vista Hospital, Sharp Coronado Hospital, Sharp Grossmont Hospital, Sharp Mary Birch Hospital, Tri-City Medical Center, and UCSD Medical Center. We also thank all the mothers who participated in the study.

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From: Mitchell, Allen A
To: Werler, Martha M; shernan@hsph.harvard.edu
Subject: FW: NEJM Correction
Date: Monday, July 13, 2015 2:13:00 PM

Dear Martha and Sonia,

I hope this brings an end to any involvement we might have with the legal issues. I do wish you had let me know when Sander first approached you—any time there is a looming legal issue, I need to know.

Hope you are both enjoying your summers!

Best,

Allen

(Please note new telephone number)

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From: Mitchell, Allen A
Sent: Monday, July 13, 2015 2:09 PM
To: 'lesdomes@g.ucla.edu'
Cc: Louik, Carol; shernan@hsph.harvard.edu; Werler, Martha M
Subject: NEJM Correction

Dear Sander,

I hope all is well with you.

Carol forwarded me the email exchanges below; since you had initially written to Sonia and Martha, and then Carol, I would have hoped that you would have included me as well.

To respond to your note:

First, let me reflect my personal perspective that the slavish worship of the dichotomous p-value is something we have fought fiercely, including with journals to which we submit our work. In that regard, I was delighted to see that Justice Sotomayor (writing for a unanimous court—how's that for an outlier?) noting the fallacy surrounding devotion to the p-value. While you and I may or may not hold similar views about the role of scientists in litigation, as a matter of longstanding policy we

make every effort to avoid becoming engaged in any litigation that involves our work.

Second, our response to Steve's inquiry had nothing at all to do with his involvement in litigation (which he disclosed, though he did not indicate for whom he was working). The simple fact was that he raised a question about a CI we published, and on careful re-examination, we found that we had indeed erred. We submitted a correction to the NEJM, and we provided the corrected information to Steve. As is the case for any of our published work, we cannot control how that information is used, including in judicial proceedings.

We let our publications speak for themselves and do not respond to the infinite number of questions that may be of interest to litigants and that might draw us into these legal proceedings.

Best regards,

Allen
(Please note new telephone number)

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From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Thursday, July 09, 2015 11:50 AM
To: Hernandez-Diaz, Sonia; Werler, Martha M; Louik, Carol
Subject: Re: correction to

Hi Sonia (and Martha and Carol),

Take a look at the exhibit 82 I sent - as you can see the defense expert obtained the results from Alan on request, and used them to place enormous stock in their "nonsignficance" and the confidence interval excluding or including 1. The e-mail exchange with Alan follows the exxpert's statement to the court.

Statisticians and epidemiologists freely present opinions in these legal documents that pander to the testing fetish even though they wouldn't dare do that in one of our journals (and wouldn't even be allowed to in Epidemiology), and the Supreme Court itself has rejected that standard (see last attachment). Still, the judge in this case puts great stock in the magic 0.05 so I am copying this material to Carol.

Carol, I would be very grateful if you could supply the additional digit to the

sertraline-septal defect.

With best wishes and thanks in advance,

Sander

On 7/9/2015 1:42 AM, Hernandez-Diaz, Sonia wrote:

> Dear Sander,
> Carol Louik run the analyses and provided the estimates. I do not know the decimal points.
>
> I understand this is important for the lawyers and that numbers should be accurate. However, I hope the decision to whether consider Sertraline guilty or not is not based on a decimal point from one observational study. Please see the BMJ publication from today concluding there are no increased risks associated with Sertraline.
> This topic is the Cape Horn of epidemiologic (conflicting) evidence, I am so glad you are involved in the discussion.
>
> All the best,
> Sonia
>
> ---
>
> **From:** Sander Greenland [mailto:lesdomes@g.ucla.edu]
> **Sent:** Wednesday, July 08, 2015 4:02 PM
> **To:** Hernandez-Diaz, Sonia; Werler, Martha M
> **Subject:** correction to
>
> Dear Sonia and Martha,
>
> Sorry to bother you with this request, but I got a call from a plaintiff lawyer (Mark Robinson) who consults me on occasion, this time on in a case involving sertraline and septal defects. I'm told I am not a named expert in this case, but he wanted to know if the statistical significance changed due to the correction to the odds-ratio estimate of 2.0 (1.2, 4.0) highlighted in Table 2 of the attached 2007 article on which you are coauthors.
>
> The defense expert, Steve Kimmel, had contacted Alan Mitchell last month about it and got back the correction shown in the attached e-mail exchange.
>
> Alan supplied the defense expert with the correction showing 2.0 (1.0,4.0). Unsurprisingly, the big question it has raised is what are the results to two digits past the decimal point, particularly what is the lower limit out to one more digit?

Alan said in the e-mails to Kimmel that he would be consulting with his coauthors, so I am writing to ask if either of you can state the estimate in more detail?

Again, apologies for bothering you with this request, but I was told Alan is away right now, and I am curious myself about the answer given the capital that Kimmel seems to have made of it (as you can see in the attached exhibit).
I hope it is an easy question to answer given that Alan mentioned having retrieved the original files in his response to Kimmel.

Thanking you in advance,
All the Best,
Sander

From: Mitchell, Allen A
To: Lin, Angela E.,M.D.; Louik, Carol; Werler, Martha M
Subject: RE: Resolution of NEJM correction
Date: Monday, July 13, 2015 3:06:00 PM

I know—but didn't want to embarrass her!

(Please note new telephone number)

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From: Lin, Angela E.,M.D. [mailto:ALIN@partners.org]
Sent: Monday, July 13, 2015 3:02 PM
To: Mitchell, Allen A; Louik, Carol; Werler, Martha M; Sheila Heitzig (AAAAI)
Subject: RE: Resolution of NEJM correction

FYI: typo **a doubling of the risk of sepatal defects, and In sofar**

From: Mitchell, Allen A [mailto:allenmit@bu.edu]
Sent: Monday, July 13, 2015 2:44 PM
To: Louik, Carol; Werler, Martha M; Sheila Heitzig (AAAAI); Lin, Angela E.,M.D.
Subject: Resolution of NEJM correction

See below.
(Please note new telephone number)

Allen A. Mitchell, M.D.
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From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Monday, July 13, 2015 1:06 PM
To: Mitchell, Allen A
Cc: Galloway, Neil; Louik, Carol
Subject: Re:

Allan,
This sounds reasonable.Thanks again.
Will pass this right along.

Caren

On Jul 13, 2015, at 12:44 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

Dear Caren,

I had a chance to review the proposed revisions with Carol, and given the Journal's position on the value of p-values, we can accept virtually all the revisions you highlighted in bold. The only one of concern relates to the following :

Page 2680, first column, text beginning with "classification of heart defects…" The OR was stated here, but without any reference to the CI or statistical significance, so we think it can remain as is.
I see your point, but in sofar as other ORS that were higher than 2 but not statistically significant were not mentioned here, inclined to remove " a doubling of the risk of sepatal defects associated with sertraline use (OR2.0, based on 13 exposed subjects, and .."

First, we were pleased to see your statement that you were "inclined to remove…", leaving (we hope) an opportunity to convince you otherwise. You are correct that we did not mention other risks that were higher than 2-fold but not statistically significant, but we did indeed mention the one risk we observed in Tables 2 and 3 that had a lower bound of 1.0: On p. 2679, first column, "Exploratory Analyses", line 8, states " One association, that between paroxetine use and undescended testis, had a lower confidence bound of 1.0." Of interest, on page 2680, column 1, line 7, we noted that our "significant" finding for paroxetine and RVOTO was supported by a finding of borderline significance in the companion CDC report: "The latter finding is supported by an odds ratio of 2.5, based on seven exposed subjects (95% CI, 1.0 to 9.6), identified by Alwan et al in an article in this issue of the *Journal*." For reasons of consistency, then, we would ask that the text at the top of column 1, page 2680, be modified to the following (the modification in bold): "…we found a doubling of the risk of septal defects associated with sertraline use (odds ratio, 2.0**, lower confidence bound 1.0**), based on 13 exposed subjects…"

Please let me know what you think, and thank you very much for giving consideration to our perspectives.

Best,

Allen
(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue

Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Thursday, July 09, 2015 10:35 AM
To: Mitchell, Allen A; Galloway, Neil
Subject:

Allan-
We discussed as a group and feeling was that we needed to remove emphasis on findings that did not meet "formal" criteria for stat significance.. (to concord with usual reporting, but also because concerned about a lack of internal consistency if continue to highlight the sertraline risk, but then not other risks that appear elevated but not significant (eg LVOT obstruction with any SSRI..) .
See comments in bold below and let me know if you agree with these changes.
Once you let me know, we will pass along for correction.
Thanks again,
Caren

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 5:00 PM
To: Mitchell, Allen A
Subject: Re: RE:

Allan-
Of course I recognize that a lower bound of something like 0.97 would not really be too different from a lower bound of something like 1.02 , but strictly speaking one would be "significant" while other wouldn't per usual criteria. So useful to let me know the actual value that was rounded to 1.0. (even though again I appreciate that arbitrary distinction..)
Thanks again.

On Jul 1, 2015, at 3:47 PM, Mitchell, Allen A <allenmit@bu.edu> wrote:

> Dear Caren,
>
> Thanks for your note. We were not aware that the online version would be corrected, and of course we agree that all aspects of the text that make reference to the erroneous CI should be modified. Just to be clear, the lower bound changed from 1.2 to 1.0—the latter reflecting what many could call "borderline significance". Below are the sections of the text that mention or reflect the erroneous CI:
>
> **Abstract: Results, beginning with "Analyses of the associations…"** We seek guidance from you; as you know, we prefer to avoid the term "significant", but recognize this may not be a shared view. If you feel strongly that only "statistically significant" associations should be

listed, **the portion of the sentence that includes "and septal defects (odds ratio, 2.0; 95% CI 1.0 to 4.0; 13 exposed subjects)" should be removed**; if you were comfortable replacing "significant associations" with "elevated risks", the reference to septal defects could remain, with the CI corrected.

Ms, page 2678, second column of text, last sentence: Again, we seek your guidance. The text beginning with "and two risk estimates had lower bounds that exceeded 1.0 .." could be changed to "…lower bounds of 1.0 or greater:" which would allow the sertraline estimate to remain**. Alternatively, if you wish to retain the "…lower bounds that exceeded 1.0:", the sertraline estimate would be removed and the preceding text would change from "…and two risk estimates.." to "and one risk estimate…"**

Page 2680, first column, text beginning with "classification of heart defects…" The OR was stated here, but without any reference to the CI or statistical significance, so we think it can remain as is.
I see your point, but in sofar as other ORS that were higher than 2 but not statistically significant were not mentioned here, inclined to remove " a doubling of the risk of sepatal defects associated with sertraline use (OR2.0, based on 13 exposed subjects, and .."

Second para, beginning with "Our observations…" Here we feel the word "significant" could be removed without changing the rest of the sentence, since the point we are trying to make is the variation in ORs, not necessarily whether they are "statistically significant".
Alternatively what about changing selected cardiac defects to "selected defects" (which then may refer also so omphalocele)?

Same page, second column, last line, beginning with "On the other hand…". This text remains **accurate if changed from "none of which" to "neither of which",**since paroxetine was "significantly" associated with right ventricular outflow tract obstruction and sertraline with omphalocele.

As you must know, we clearly regret this error, and appreciate your efforts in assuring that we set the record straight. We look forward to hearing back from you.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, July 01, 2015 12:11 PM
To: Mitchell, Allen A
Cc: Galloway, Neil; Morrissey, Stephen
Subject:

Dear Allen,
I hope you are doing well.
Mike forwarded your inquiry regarding a correction to your 2007 manuscript.
Unfortunately, making this correction will involve a few more changes than simply publishing the letter that you attached (I pasted below). To make sure the article is correct on line, we need to make change in each place in the article that the lower bound of the confidence interval was mentioned , and also need to change the associated interpretation (including in abstract) if this has changed (ie if the lower bound of "1.0" was actually slightly lower than 1 and thus no longer statistically significant using a 2 sided p value < 0.05?) Please send me a summary of all places (in order) where changes need to be made, and provide original wording/numbers and then wording/numbers that should replace.
Once you send this information, we can process correction.
Thank you in advance,

Caren

In response to an inquiry from a colleague regarding our paper "First-Trimester Use of Selective Serotonin-Reuptake Inhibitors and the Risk of Birth Defects" (NEJM ref), we discovered an error in Table 2. In that table, we reported an adjusted odds ratio for sertraline exposure in relation to septal defects as 2.0 with a 95% confidence interval of 1.2-4.0. On review of the original data tables, we confirmed that the odds ratio is correct as originally reported; however, due to a transcription error, the lower bound of the confidence interval should actually be 1.0 rather than 1.2. We have confirmed that all other entries in the table are correct as originally published.

We apologize for the error.

Sincerely,
Carol Louik etc.

This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

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by return email and delete the original message from all computer systems. Thank you.

From: Kaufman, David W
To: Mitchell, Allen A; Rosenberg, Lynn A; Palmer, Julie R; Vezina, Richard
Subject: RE: Sander
Date: Wednesday, July 15, 2015 2:08:46 PM

Definitely a good idea to get a legal opinion on this. Very important not to increase the subpoena risk. And I agree there is no reason to keep the heat on by responding quickly. Glad to discuss whenever if that would help.

David

From: Mitchell, Allen A
Sent: Wednesday, July 15, 2015 1:59 PM
To: Rosenberg, Lynn A; Kaufman, David W; Palmer, Julie R; Vezina, Richard
Subject: RE: Sander

Thanks for your note and thoughts, Lynn. I have already considered what you propose, though I'm not sure we need to provide any further data to parties in the suit, lest we open ourselves up to subpoena (despite his assertion that we're already involved). Further, he is acting as a lawyer, not a scientist, in his selective citations. First, we noted federal support for BDS, but it was "in part", with the analysis funded by GSK. Second, while he took the time to count how often we used "stat signif" in some papers, he neglected to note the many where we did not. The point he wishes to make could be made without invoking any of our own data. However, before I respond to him, I am seeking legal advice from BU, as I don't want to fall into any traps. I certainly have no plans to respond quickly—unlike Sander, I have many more pressing issues to occupy my time!

I would likely seek the gang's advice going forward.

Thanks again,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Rosenberg, Lynn A
Sent: Wednesday, July 15, 2015 1:49 PM
To: Mitchell, Allen A; Kaufman, David W; Palmer, Julie R; Vezina, Richard
Subject: Sander

Dear Allen,
You have my condolences. Very bad timing. Also, not a good person to have a disagreement with. I'd

be happy to discuss this with you and the group, but in case you're not up for that or have already decided what to do, here's my unasked for opinion. I don't think you can make a convincing case for not providing Sander with the 2-digit confidence interval that you derived from a publicly funded study. You and Sander share views about statistical significance. It would be good to end what has unwittingly become a battle—and one way to do that would be to take up his offer to together submit views you agree with to the court.
Lynn

Lynn Rosenberg, ScD
Associate Director
Slone Epidemiology Center at Boston University
Tel 617 2066181
Fax 617 7385119

From: Mitchell, Allen A
Sent: Wednesday, July 15, 2015 11:11 AM
To: Rosenberg, Lynn A; Kaufman, David W; Palmer, Julie R
Subject: FW: NEJM Correction

I share this with you seeking your pity—like I really need this right now!

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Tuesday, July 14, 2015 9:51 PM
To: Mitchell, Allen A
Cc: Louik, Carol; shernan@hsph.harvard.edu; Werler, Martha M; Lin, Angela E.,M.D.
Subject: Re: NEJM Correction

Dear Allen,

I apologize for not writing you initially, but I asked Sonia and Martha for the information because I was told you were unavailable and I know them both personally. I was then told Carol, not you, had the information. No slight to you was intended and I regret that you took it that way.

I am now surprised and deeply disturbed that you have refused my request,

especially since Kimmel did not submit his request to everyone on the paper either, and I can see no labor, confidentiality, legal or embargo issue involved here to justify withholding this tiny bit of information. So your withholding the data seems to me to be a personal slight, as well as an ethical mistake as I will now explain.

In my collaborations we do not need permission to supply such purely statistical details like this to requestors, because we think that should be a matter of public record - especially when the study was paid for by the public (listed on the study are NICHHD and NHLBI). Apparently you view these details differently, incommensurable with views that such data are not yours but information which you were paid to obtain and analyze in order to supply vital information to the public - which includes courts and other branches of government.

Your comment about p-values is also disturbing insofar as you say "the slavish worship of the dichotomous p-value is something we have fought fiercely" yet Louik et al. 2007 uses "significance" or its variants to refer to dichotomized P-values no less than 3 times in the abstract and 9 times in the remaining text. I decided to check one of your 2015 studies ("Maternal hypertensive disorders,antihypertensive medication use, and the risk of birth defects: a case–control study") and was pleased to see that statistical "significance" was used only 5 times, so perhaps you will achieve internal victory over dichotomization by 2020. Meanwhile, I've done my share for the cause of extirpating significance abuse in the legal arena and elsewhere, as the 5 attached example articles illustrate.

You responded quickly to Steve Kimmel's inquiry even though his e-mail made clear it was litigation motivated. We all can see exactly how Steve Kimmel used the information - Please read the first page of the attached:, he used it precisely for the type of dichotomy abuse you say you decry, quoting your e-mail directly in his defense report. Thus it is your prompt aid to defense which created the need for my request, which was based on what may be seen as Kimmel's misrepresentation of facts which you supplied.

In other words, my request is not a random one for some isolated case, but one produced by your own actions. Thus I find it difficult to comprehend how you can claim to distance yourself in this matter by denying information to a colleague after your aid to a litigant. And frankly, Allen, if the more precise result would not support his claim of nonsignficance, by refusing requests for this detail you are now abetting defense misrepresentation to the court of your actual results. In any event, the precise results may well become public along with the correspondence via subpoena, so I'm afraid you are already involved in this case, like it or not.

I'd be happy to let our correspondence and the attached correspondence stand (along with the precise result when it becomes available) as a matter of public record for

others to infer what principles you were applying and violating in denying my request. However, before this matter goes to public review, I'll propose what I hope is an amicable and constructive solution: I was preparing to submit the information in an *amicus* brief to the court (recall that I am not an expert in this case). Together we could all author this *amicus* brief in which we (rather than discovering attorneys) supply the detail and explain that it should not be interpreted based on whether 1 exactly falls in or out of the interval. I am completely open on the precise wording as long as the crucial information is conveyed to the court but here is how I thought that brief could go (I have omitted citations for now but obviously Modern Epidemiology and writings by me and collaborators would be among them):

It has come to our attention that a supplementary report filed in this matter [cite] has reported that the corrected confidence interval of 1.0-4.0 from the study by Louik et al. (2007) for the adjusted association of sertraline (Zoloft) and septal defects no longer includes 1 and thus cannot be considered "statistically significant."

We hereby wish to advise the court that although this is a technically [inaccurate/accurate] description insofar as the interval expressed with greater precision is ?.??-?.??, decisions based on the significance or nonsignificance of single studies are inappropriate, as has been widely documented in the methodologic literature [cites]. Among the reasons are that proper combination of statistical results requires the presentation and interpretation of evidence from each study along a continuum, not as a dichotomy of significant/nonsignificant. The latter dichotomy is highly misleading because it discards essential information about how strongly or weakly the evidence from each study supports or conflicts with the hypothesis being tested. A common continuous measure is the P-value, which in this case happens to be 0.0??. Whether it happens to fall slightly above or below the usual 0.05 threshold of "significance" is irrelevant to this measure, for the study alone is not a proper basis for any decision; in particular, statistical tests are designed to be applied to the totality of available statistical evidence, not applied and then combined after the fact. Thus the results of Louik et al. need to be combined with other evidence to properly evaluate the material as well as statistical significance of the overall evidence.

The need to go beyond statistical significance when considering evidence has been affirmed by a rare unanimous opinion by the Supreme Court of the United States [Matrixx]. We strongly urge the court in the present case to study this decision in detail, and to modify its current application of significance criteria to apply only to overall evidence, not individual studies. Such a modification would bring the deliberations in this case into line with the Supreme Court opinion and also align with current recommendations in the peer-reviewed literature and leading textbooks on evidence synthesis [cites]."

I would be honored if you would join me in creating and filing this brief. Again I

intend the invitation to all authors of the original paper who might be interested and in agreement with these points. In fact others in agreement could join if you felt comfortable with that (I was thinking of Ken Rothman in particular).

Sincerely,
Sander

On 7/13/2015 11:09 AM, Mitchell, Allen A wrote:

> Dear Sander,
>
> I hope all is well with you.
>
> Carol forwarded me the email exchanges below; since you had initially written to Sonia and Martha, and then Carol, I would have hoped that you would have included me as well.
>
> To respond to your note:
>
> First, let me reflect my personal perspective that the slavish worship of the dichotomous p-value is something we have fought fiercely, including with journals to which we submit our work. In that regard, I was delighted to see that Justice Sotomayor (writing for a unanimous court—how's that for an outlier?) noting the fallacy surrounding devotion to the p-value. While you and I may or may not hold similar views about the role of scientists in litigation, as a matter of longstanding policy we make every effort to avoid becoming engaged in any litigation that involves our work.
>
> Second, our response to Steve's inquiry had nothing at all to do with his involvement in litigation (which he disclosed, though he did not indicate for whom he was working). The simple fact was that he raised a question about a CI we published, and on careful re-examination, we found that we had indeed erred. We submitted a correction to the NEJM, and we provided the corrected information to Steve. As is the case for any of our published work, we cannot control how that information is used, including in judicial proceedings.
>
> We let our publications speak for themselves and do not respond to the infinite number of questions that may be of interest to litigants and that might draw us into these legal proceedings.
>
> Best regards,
>
> Allen
> **(Please note new telephone number)**
>
> Allen A. Mitchell, M.D.

Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Thursday, July 09, 2015 11:50 AM
To: Hernandez-Diaz, Sonia; Werler, Martha M; Louik, Carol
Subject: Re: correction to

Hi Sonia (and Martha and Carol),

Take a look at the exhibit 82 I sent - as you can see the defense expert obtained the results from Alan on request, and used them to place enormous stock in their "nonsignficance" and the confidence interval excluding or including 1. The e-mail exchange with Alan follows the exxpert's statement to the court.

Statisticians and epidemiologists freely present opinions in these legal documents that pander to the testing fetish even though they wouldn't dare do that in one of our journals (and wouldn't even be allowed to in Epidemiology), and the Supreme Court itself has rejected that standard (see last attachment). Still, the judge in this case puts great stock in the magic 0.05 so I am copying this material to Carol.

Carol, I would be very grateful if you could supply the additional digit to the sertraline-septal defect.

With best wishes and thanks in advance,

Sander

On 7/9/2015 1:42 AM, Hernandez-Diaz, Sonia wrote:

> Dear Sander,
> Carol Louik run the analyses and provided the estimates. I do not know the decimal points.
>
> I understand this is important for the lawyers and that numbers should be accurate. However, I hope the decision to whether consider Sertraline guilty or not is not based on a decimal point from one observational study. Please see the BMJ publication from today concluding there are no increased risks associated with Sertraline.

This topic is the Cape Horn of epidemiologic (conflicting) evidence, I am so glad you are involved in the discussion.

All the best,
Sonia

From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Wednesday, July 08, 2015 4:02 PM
To: Hernandez-Diaz, Sonia; Werler, Martha M
Subject: correction to

Dear Sonia and Martha,

Sorry to bother you with this request, but I got a call from a plaintiff lawyer (Mark Robinson) who consults me on occasion, this time on in a case involving sertraline and septal defects. I'm told I am not a named expert in this case, but he wanted to know if the statistical significance changed due to the correction to the odds-ratio estimate of 2.0 (1.2, 4.0) highlighted in Table 2 of the attached 2007 article on which you are coauthors.

The defense expert, Steve Kimmel, had contacted Alan Mitchell last month about it and got back the correction shown in the attached e-mail exchange.

Alan supplied the defense expert with the correction showing 2.0 (1.0,4.0). Unsurprisingly, the big question it has raised is what are the results to two digits past the decimal point, particularly what is the lower limit out to one more digit? Alan said in the e-mails to Kimmel that he would be consulting with his coauthors, so I am writing to ask if either of you can state the estimate in more detail?

Again, apologies for bothering you with this request, but I was told Alan is away right now, and I am curious myself about the answer given the capital that Kimmel seems to have made of it (as you can see in the attached exhibit). I hope it is an easy question to answer given that Alan mentioned having retrieved the original files in his response to Kimmel.

Thanking you in advance,

All the Best,
Sander

From: Mitchell, Allen A
To: Sander Greenland
Cc: Louik, Carol; shernan@hsph.harvard.edu; Werler, Martha M; Lin, Angela E.,M.D.
Subject: RE: NEJM Correction
Date: Wednesday, July 15, 2015 2:50:00 PM

Dear Sander,

I am in the midst of some very pressing activities and will be leaving on vacation Friday. I wanted you to know that I will carefully review your note and get back to you.

Best,

Allen

(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Tuesday, July 14, 2015 9:51 PM
To: Mitchell, Allen A
Cc: Louik, Carol; shernan@hsph.harvard.edu; Werler, Martha M; Lin, Angela E.,M.D.
Subject: Re: NEJM Correction

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I am now surprised and deeply disturbed that you have refused my request, especially since Kimmel did not submit his request to everyone on the paper either, and I can see no labor, confidentiality, legal or embargo issue involved here to justify withholding this tiny bit of information. So your withholding the data seems to me to be a personal slight, as well as an ethical mistake as I will now explain.

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Your comment about p-values is also disturbing insofar as you say "the slavish worship of the dichotomous p-value is something we have fought fiercely" yet Louik et al. 2007 uses "significance" or its variants to refer to dichotomized P-values no less than 3 times in the abstract and 9 times in the remaining text. I decided to check one of your 2015 studies ("Maternal hypertensive disorders,antihypertensive medication use, and the risk of birth defects: a case–control study") and was pleased to see that statistical "significance" was used only 5 times, so perhaps you will achieve internal victory over dichotomization by 2020. Meanwhile, I've done my share for the cause of extirpating significance abuse in the legal arena and elsewhere, as the 5 attached example articles illustrate.

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In other words, my request is not a random one for some isolated case, but one produced by your own actions. Thus I find it difficult to comprehend how you can claim to distance yourself in this matter by denying information to a colleague after your aid to a litigant. And frankly, Allen, if the more precise result would not support his claim of nonsignficance, by refusing requests for this detail you are now abetting defense misrepresentation to the court of your actual results. In any event, the precise results may well become public along with the correspondence via subpoena, so I'm afraid you are already involved in this case, like it or not.

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is how I thought that brief could go (I have omitted citations for now but obviously Modern Epidemiology and writings by me and collaborators would be among them):

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We hereby wish to advise the court that although this is a technically [inaccurate/accurate] description insofar as the interval expressed with greater precision is ?.??-?.??, decisions based on the significance or nonsignificance of single studies are inappropriate, as has been widely documented in the methodologic literature [cites]. Among the reasons are that proper combination of statistical results requires the presentation and interpretation of evidence from each study along a continuum, not as a dichotomy of significant/nonsignificant. The latter dichotomy is highly misleading because it discards essential information about how strongly or weakly the evidence from each study supports or conflicts with the hypothesis being tested. A common continuous measure is the P-value, which in this case happens to be 0.0??. Whether it happens to fall slightly above or below the usual 0.05 threshold of "significance" is irrelevant to this measure, for the study alone is not a proper basis for any decision; in particular, statistical tests are designed to be applied to the totality of available statistical evidence, not applied and then combined after the fact. Thus the results of Louik et al. need to be combined with other evidence to properly evaluate the material as well as statistical significance of the overall evidence.

The need to go beyond statistical significance when considering evidence has been affirmed by a rare unanimous opinion by the Supreme Court of the United States [Matrixx]. We strongly urge the court in the present case to study this decision in detail, and to modify its current application of significance criteria to apply only to overall evidence, not individual studies. Such a modification would bring the deliberations in this case into line with the Supreme Court opinion and also align with current recommendations in the peer-reviewed literature and leading textbooks on evidence synthesis [cites]."

I would be honored if you would join me in creating and filing this brief. Again I intend the invitation to all authors of the original paper who might be interested and in agreement with these points. In fact others in agreement could join if you felt comfortable with that (I was thinking of Ken Rothman in particular).

Sincerely,
Sander

On 7/13/2015 11:09 AM, Mitchell, Allen A wrote:

Dear Sander,

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To respond to your note:

First, let me reflect my personal perspective that the slavish worship of the dichotomous p-value is something we have fought fiercely, including with journals to which we submit our work. In that regard, I was delighted to see that Justice Sotomayor (writing for a unanimous court—how's that for an outlier?) noting the fallacy surrounding devotion to the p-value. While you and I may or may not hold similar views about the role of scientists in litigation, as a matter of longstanding policy we make every effort to avoid becoming engaged in any litigation that involves our work.

Second, our response to Steve's inquiry had nothing at all to do with his involvement in litigation (which he disclosed, though he did not indicate for whom he was working). The simple fact was that he raised a question about a CI we published, and on careful re-examination, we found that we had indeed erred. We submitted a correction to the NEJM, and we provided the corrected information to Steve. As is the case for any of our published work, we cannot control how that information is used, including in judicial proceedings.

We let our publications speak for themselves and do not respond to the infinite number of questions that may be of interest to litigants and that might draw us into these legal proceedings.

Best regards,

Allen
(Please note new telephone number)

Allen A. Mitchell, M.D.
Director, Slone Epidemiology Center
Professor of Epidemiology and Pediatrics
Boston University Schools of Public Health and Medicine
1010 Commonwealth Avenue
Boston, MA 02215
allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119

From: Sander Greenland [mailto:lesdomes@g.ucla.edu]
Sent: Thursday, July 09, 2015 11:50 AM
To: Hernandez-Diaz, Sonia; Werler, Martha M; Louik, Carol
Subject: Re: correction to

Hi Sonia (and Martha and Carol),

Take a look at the exhibit 82 I sent - as you can see the defense expert obtained the results from Alan on request, and used them to place enormous stock in their "nonsignficance" and the confidence interval excluding or including 1. The e-mail exchange with Alan follows the exxpert's statement to the court.

Statisticians and epidemiologists freely present opinions in these legal documents that pander to the testing fetish even though they wouldn't dare do that in one of our journals (and wouldn't even be allowed to in Epidemiology), and the Supreme Court itself has rejected that standard (see last attachment). Still, the judge in this case puts great stock in the magic 0.05 so I am copying this material to Carol.

Carol, I would be very grateful if you could supply the additional digit to the sertraline-septal defect.

With best wishes and thanks in advance,

Sander

On 7/9/2015 1:42 AM, Hernandez-Diaz, Sonia wrote:

> Dear Sander,
> Carol Louik run the analyses and provided the estimates. I do not know the decimal points.
>
> I understand this is important for the lawyers and that numbers should be accurate. However, I hope the decision to whether consider Sertraline guilty or not is not based on a decimal point from one observational study. Please see the BMJ publication from today concluding there are no increased risks associated with Sertraline.
> This topic is the Cape Horn of epidemiologic (conflicting) evidence, I am so glad you are involved in the discussion.
>
> All the best,
> Sonia
>
> ---
>
> **From:** Sander Greenland [mailto:lesdomes@g.ucla.edu]
> **Sent:** Wednesday, July 08, 2015 4:02 PM

To: Hernandez-Diaz, Sonia; Werler, Martha M
Subject: correction to

Dear Sonia and Martha,

Sorry to bother you with this request, but I got a call from a plaintiff lawyer (Mark Robinson) who consults me on occasion, this time on in a case involving sertraline and septal defects. I'm told I am not a named expert in this case, but he wanted to know if the statistical significance changed due to the correction to the odds-ratio estimate of 2.0 (1.2, 4.0) highlighted in Table 2 of the attached 2007 article on which you are coauthors.

The defense expert, Steve Kimmel, had contacted Alan Mitchell last month about it and got back the correction shown in the attached e-mail exchange.

Alan supplied the defense expert with the correction showing 2.0 (1.0,4.0). Unsurprisingly, the big question it has raised is what are the results to two digits past the decimal point, particularly what is the lower limit out to one more digit? Alan said in the e-mails to Kimmel that he would be consulting with his coauthors, so I am writing to ask if either of you can state the estimate in more detail?

Again, apologies for bothering you with this request, but I was told Alan is away right now, and I am curious myself about the answer given the capital that Kimmel seems to have made of it (as you can see in the attached exhibit). I hope it is an easy question to answer given that Alan mentioned having retrieved the original files in his response to Kimmel.

Thanking you in advance,
All the Best,
Sander

Begin forwarded message:

From: Sander Greenland <lesdomes@g.ucla.edu>
Date: July 21, 2015 at 3:36:58 PM EDT
To: "Mitchell, Allen A" <allenmit@bu.edu>
Cc: "Louik, Carol" <clouik@bu.edu>, "shernan@hsph.harvard.edu" <shernan@hsph.harvard.edu>, "Werler, Martha M" <werler@bu.edu>, "Lin, Angela E.,M.D." <ALIN@PARTNERS.ORG>
Subject: Re: NEJM Correction

Dear Allen,

I've been told that the defense has been informed about and is requesting these e-mails, so it appears that our exchange (as well as the results you withheld) will likely become public record before long.

Best,
Sander

On 7/15/2015 11:50 AM, Mitchell, Allen A wrote:

> Dear Sander,
>
> I am in the midst of some very pressing activities and will be leaving on vacation Friday. I wanted you to know that I will carefully review your note and get back to you.
>
> Best,
>
> Allen
>
> **(Please note new telephone number)**
>
> Allen A. Mitchell, M.D.
> Director, Slone Epidemiology Center
> Professor of Epidemiology and Pediatrics
> Boston University Schools of Public Health and Medicine
> 1010 Commonwealth Avenue
> Boston, MA 02215
> allenmit@bu.edu; **phone 617 206 6210**; fax 617 738 5119